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The Graduate School of the University of Minnesota

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The Mayo Foundation

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I

1915-1920

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PREFACE

It is believed that many of the articles herein contain new material which will prove of real interest both to clinicians and investigators. Subsequent volumes will probably contain continuations of many of these studies since quite naturally in the same institutions research is apt to follow along certain lines for several years although it may be participated in by many different individuals. The clinical analyses will cover especially the clinical material most available. Thus, the volume from year to year will present detailed studies, principally by the younger members of the staff, of the clinical material available in the Mayo Clinic and in the hospitals controlled by the Medical School of the University of Minnesota. To these studies will be added the results of research work in the preclinical medical sciences from both medical departments of the Graduate School. The subject matter will be confined to the sources indicated with the occasional addition of contributions from members of the faculty on subjects which are related to those discussed by graduate students.

The first obligation of a true university, that which makes it a university and not an aggregation of colleges, is to stimulate research, to attack unsolved problems, to train its best students to ask and to answer questions. Its second obligation is to make available the results of these investigations, the answers to these questions. The second obligation the University of Minnesota attempts to meet in this volume and in doing it to give evidence of its good faith in seeking to discharge the first in the field of medical science, for these papers summarize most of the research work by the graduate students in the medical department of the Graduate School in the University of Minnesota during the years 1915 to 1920 inclusive. Nearly all of the papers were originally in the form of theses presented by graduate medical students in the Mayo Foundation and the Medical School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science or Doctor of Philosophy in various preclinical as well as clinical fields. The theses are published either in full or in abstract. In addition the volume contains abstracts of a few papers by graduate medical students which were not presented as theses. Some of the theses and papers have been previously published in current literature. The abstracts have been made by the authors. All articles have been passed on by the committee named below, who have also called to their aid other members of the faculty.

Publication Committee:

Louis Blanchard Wilson, M. D., Director of The Mayo Foundation, Chairman.

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Leonard George Rowntree, M. D., Professor of Medicine.

Clarence Martin Jackson, M. D., Professor of Anatomy.

Julius Parker Sedgwick, M. D., Professor of Pediatrics.

Mrs. Maud H. Mellish, Editor.

November, 1921

LIST OF CONTRIBUTORS*

ADAIR, FRED L., B.S., M.D., M.A., Associate Professor of Obstetrics and Gynecology, The Medical School.

ADSON, ALFRED W., B.S., M.D., M.A., M.S. in Surgery, Fellow in Surgery, The Mayo Foundation.

ALLEN, WILLIAM F., B.A., M.A., Ph.D., Instructor in Anatomy, The Medical School.

BARRY, LEE W., M.D., Ph.D. in Obstetrics and Gynecology, Fellow in Obstetrics and Gynecology, The Medical School.

BAUMGARTNER, EDWIN A., B.A., M.A., Ph.D., Instructor in Anatomy, The Medical School.

BENTON, ANNE GERTRUDE, B.A., M.A., Instructor in Bacteriology, The Medical School.

BERKMAN, DAVID M., B.S., M.D., M.S. in Medicine, Fellow in Medicine, The Mayo Foundation.

BRODERS, ALBERT C., M.D., M.S. in Pathology, Fellow in Pathology, The Mayo Foundation.

BUMPUS, HERMON C., Ph.B., M.D., M.S. in Urology, Fellow in Urology, The Mayo Foundation.

BUTSCH, JOHN L., B.S., M.D., M.S., Ph.D. in Surgery, Fellow in Surgery, The Mayo Foundation.

CALKINS, LEROY A., B.S., M.D., M.S. in Obstetrics and Gynecology, Fellow in Obstetrics and Gynecology, The Medical School.

CAMP, WALTER E., B.A., M.D., M.A., Instructor in Anatomy, The Medical School.

CRISPIN, EGERTON L., Ph.B., M.D., M.S. in Medicine, Fellow in Medicine, The Mayo Foundation.

DEDERER, CARLETON, B.A., M.D., M.S. in Experimental Surgery, Fellow in Surgery, The Mayo Foundation.

DRIPS, DELLA GAY, B.S., M.S., Fellow in Pathology, The Mayo Foundation.

DUNN, HALBERT L., B.A., M.A., Fellow in Anatomy, The Medical School.

FINEMAN, BERTHA CECELIA, B.A., M.S., Fellow in Bacteriology, The Medical School.

GAULT, CHARLES C., B.A., M.A., Instructor in Physiology, The Medical School.

GREEN, ROBERT G., B.A., M.A., Assistant in Bacteriology, The Medical School.

---

* The degrees and titles here listed are those held by the contributors on the conferring of the degrees for the theses.

Gunby, Paul C., B.A., M.D., Fellow in Surgery, The Mayo Foundation.

Harrington, Stuart W., M.D., M.S. in Surgery, Fellow in Surgery, The Mayo Foundation.

Hedblom, Carl A., B.A., M.A., M.D., Ph.D. in Surgery, Fellow in Surgery, The Mayo Foundation.

Herrmann, Siegfried F., B.S., M.A., Fellow in Bacteriology, The Medical School.

Horgan, Edmund J., M.D., M.S. in Surgery, Fellow in Surgery, The Mayo Foundation.

*Hoskins, Elmer R., B.A., M.A., Ph.D., Instructor in Anatomy, The Medical School.

Hunt, Verne C., B.S., M.D., M.S. in Surgery, Fellow in Surgery, The Mayo Foundation.

Kanda, Sakyo, M.A., Ph.D., Fellow in Physiology, The Medical School.

Kittelson, John A., B.S., M.A., Fellow in Anatomy, The Medical School.

Knapp, Frank N., M.D., M.S. in Ophthalmology, Fellow in Ophthalmology, The Medical School.

Luden, Georgine, B.A., M.A., Arzt., M.D. (Munich), Ph.D. in Pathology, Fellow in Pathology, The Mayo Foundation.

Lyons, Horace R., M.D., M.S. in Oto-Laryngology, Fellow in Oto-Laryngology, The Mayo Foundation.

*McDowell, Ivan W., M.D., M.S. in Surgery, Fellow in Surgery, The Mayo Foundation.

Mackeen, Helen Adams, B.S., M.A., Fellow in Anatomy, The Medical School.

McKinley, John C., B.S., M.A., Fellow in Anatomy, The Medical School.

McMahon, Francis B., B.S., M.D., M.S. in Surgery, Fellow in Surgery, The Mayo Foundation.

McWhorter, Golder L., B.S., M.D., Ph.D. in Surgery, Fellow in Surgery, The Medical School.

Meyerding, Henry W., B.S., M.D., M.S. in Orthopedic Surgery, Fellow in Orthopedic Surgery, The Mayo Foundation.

Moore, Charles U., B.A., M.D., M.S., Fellow in Pediatrics, The Medical School.

Morris, Ralph E., M.D., Ph.D., Fellow in Medicine, The Medical School.

Nelson, Orville N., B.S., M.S., Assistant in Bacteriology, The Medical School.

Nixon, Charles E., B.A., M.D., M.S. in Neurology, Fellow in Neurology, The Medical School.

Norris, Edgar H., B.S., M.A., Fellow in Anatomy, The Medical School.

Olson, Frederick A., B.A., M.D., M.S. in Surgery, Fellow in Surgery, The Mayo Foundation.

*Deceased.

OTT, WILLIAM O., B.S., M.D., M.S. in Surgery, Fellow in Surgery, The Mayo Foundation.

PALMER, CHARLES C., D.V.M., M.S., Graduate Student, The Medical School.

PARKER, HARRY L., B.A., M.D., Fellow in Medicine, The Mayo Foundation.

PEMBERTON, JOHN DE J., B.A., M.D., M.S. in Surgery, Fellow in Surgery, The Mayo Foundation.

PETTIBONE, DOROTHY FOSTER, B.A., M.S., Fellow in Bacteriology, The Mayo Foundation.

REEVES, THADDEUS B., B.S., M.D., M.S. in Surgery, Fellow in Surgery, The Mayo Foundation.

ROBERTS, FRANK L., B.A., M.A., Fellow in Anatomy, The Medical School.

*ROYS, CHARLES K., B.A., M.D., M.A., Fellow in Anatomy, The Medical School.

RUTLEDGE, LLOYD H., B.A., M.A., Fellow in Anatomy, The Medical School.

SANDIFORD, IRENE, B.A., Ph.D., Fellow in Medicine, The Mayo Foundation.

SHANNON, WILLIAM R., B.S., M.A., Fellow in Pathology, The Medical School.

SIPERSTEIN, DAVID M., B.S., M.A., Fellow in Anatomy, The Medical School.

STEWART, CHESTER A., B.A., M.A., Ph.D., Fellow in Anatomy, The Medical School.

STRUTHERS, JOHN E., M.D., Special Student in Surgery, The Mayo Foundation.

TAYLOR, ROOD, M.D., Ph.D. in Pediatrics, Fellow in Pediatrics, The Medical School.

TUCKER, WILLIAM J., B.A., M.A., M.D., M.S. in Surgery, Fellow in Surgery, The Mayo Foundation.

WELD, EDWARD H., B.A., M.D., M.S. in Surgery, Fellow in Surgery, The Mayo Foundation.

WEYRENS, JOSEPH P., B.S., M.D., M.S. in Surgery, Fellow in Surgery, The Mayo Foundation.

WHITE, PAUL A., B.S., Ph.B., M.D., M.S. in Surgery, Fellow in Surgery, The Mayo Foundation.

WILLIUS, FREDRICK A., B.S., M.D., M.S. in Medicine, Fellow in Medicine, The Mayo Foundation.

WOLTMAN, HENRY W., B.S., M.D., Ph.D. in Neurology, Fellow in Neurology, The Medical School.

*Deceased

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I

ALIMENTARY TRACT

THE MORPHOLOGY OF THE DIGESTIVE AND RESPIRATORY TRACTS IN A 20 MM. PIG EMBRYO*

LLOYD H. RUTLEDGE

A pig embryo 20 mm. in crown-rump length, from the Harvard embryologic collection (H.E.C. 1702), cut in transverse serial sections of 16 microns, was used as the basis for study. A series of wax reconstructions (Born's method) was made of the epithelial walls of the entire digestive and respiratory tracts, except the liver and portions of the intestine. This was supplemented by a graphic reconstruction of the entire tracts. For comparisons, in addition to dissections, several sectioned embryos of nearly the same length from the Missouri and Minnesota embryologic collections were studied. In all cases a careful microscopic study of the serial sections was made in order to determine accurately the structure and relations (including variations) and to aid in interpreting the models.

The more important points observed on the epithelial portion of the respiratory tract are as follows:

The elongated irregular nasal cavity presents three ethmoturbinal, a nasoturbinal, and a maxilloturbinal concha. In addition the concha obtecta and three frontal conchæ seem to be present.

The lateral nasal gland is represented by a small tube-like anlage connected with the cephalic (anterior) portion of the middle meatus.

The simple tube-like anlage of the nasolacrimal duct is lightly fused with the dorsal margin of the inferior meatus, ending blindly cephalad and caudad.

The larynx possesses a T-shaped lumen which is interrupted for a short distance by the prominence of the arytenoid swellings.

The bronchial tree is well branched, presenting a slightly more complicated condition than that shown by Flint in an 18.5 mm. pig.

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* Abstract of unpublished thesis presented to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Arts, 1916.

The more important points observed on the epithelial portion of the digestive tract are as follows:

The mouth is divisible into vestibulum oris and cavum oris proprium, the boundary lines being the superior and inferior dental ridges. The vestibule presents the prominent vestibular fold.

The salivary glands are represented by three anlages. The parotid anlage is a solid epithelial cord arising from the oral epithelium caudodorsad to the commissure of the lips and extending caudad. The anlage of the right side divides near its middle portion into three cords which immediately reunite. The anlage of the left side in a corresponding position presents merely a bulb-like swelling. The submaxillary anlage is the most advance of the three. It arises as a solid cord from the lingual sulcus and terminates in a gland mass just ventral to the first entodermal pouch.

The short cord-like anlage of the sublingual gland is connected to the lingual sulcus by a small epithelial plate in common with the submaxillary anlage.

The pharynx presents two entodermal pouches. The entodermal pouch on its ventral surface is fused with the ectoderm and shows a marked constriction at its base. The second pouch is less prominent, appearing as the tonsillar fold on the lateral margin of the pharynx.

The pharyngeal bursa appears as a small blind outpouching from the dorsal and caudal portions of the pharyngeal wall.

The thymus has no connection with the pharynx or the ectoderm. The right and left thoracic segments are not fused but lie in close proximity on the surface of the pericardium.

The thyroid gland is a single mass lying ventral to the trachea. The lateral elements (including parathyroid IV) derived from the fourth pouch are still distinguishable.

The esophagus is a simple tube throughout, presenting a single dorsal fold. Its wall contains numerous vacuoles but there is no bridging or obliteration of the main lumen.

The fundus of the stomach has a prominent diverticulum. The internal surface of the stomach presents a few small pits.

The dorsal and ventral pancreatic anlages are not fused, but in one of the four specimens examined their ducts were found to be in apposition at the place of crossing. The duct of the ventral pancreas has not lost its connection with the ductus choledochus. In one specimen this duct appeared double. The duct of the dorsal pancreas opens into the dorsal side of the duodenum caudad to the opening of the common bile duct.

Beside the umbilical loop, the small intestine presents two loops a short distance beyond the duodenum. The epithelial wall exhibits numerous buds and diverticula. In the duodenal region they are along the line of mesenteric attachment. Vacuoles are numerous in the jejunal region, but less common elsewhere. The lumen is very irregular but continuous throughout.

The cecum is present as a small blind pouch on the umbilical loop of the gut. The large intestine does not show loops or coils. Its lumen is slightly sacculated but patent throughout.

The rectum is compressed laterally; it has a dorsal fold, and presents two swellings. A transverse crescentic ridge on the internal surface marks the external constriction between the two swellings. A second ridge in the caudal part of the rectum may represent the remnant of the earlier anal plate.

HUNGER IN THE INFANT*

ROOD TAYLOR

Cannon and Washburn, and Carlson and his colaborers have given us a proved method for studying hunger objectively; its time of occurrence, its intensity, its effects, and the means by which it may be produced or inhibited. They have shown that contractions of the so called empty stomach cause the hunger sensation. These contractions depend in part on vagus tonus. They can be increased by chemical changes in the blood, but are primarily due to a gastric mechanism as purely automatic as is that of the heart.

Impulses set up by these contractions and carried to the higher centers are, in the normal consciousness, recognized as hunger. These impulses produce secondary effects such as restlessness and irritability. They increase the reflex excitability of the central nervous system, the heart beats faster, and there are changes in the vasomotor mechanism. Well fed, sedentary adults seldom experience hunger. The prime factor in their desire for food depends not on the basis of distress due to the contractions of a hollow viscus, but on "the memory processes of past experience with palatable foods." This psychic factor is appetite, and its absolute distinction from the physical factor, hunger, must be kept in mind.

Working on dogs, Patterson, in 1914, showed the gastric hunger contractions to be much more frequent and vigorous in young animals than in older animals. In 1915, Carlson and Ginsburg described the great intensity of hunger contractions in the human new-born. Previous to that year no productive analytic studies of the hunger sense in the human infant had been made. Appetite and hunger were not distinguished, and the sucking mechanism alone had been analyzed.

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* Thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Pediatrics, 1917.

This thesis is published in full in the American Journal of Diseases of Children, 1917, xiv, 233–257.

The bibliography is herewith omitted.

In 1888, Auerbach distinguished the infantile type of sucking from the voluntary inspiratory type employed by the adult, and in 1894 Basch, disproving the older theory of Preyer that sucking is instinctive, showed it to be entirely reflex.

Czerny, in 1893, observed that an infant awakened a short time after taking his fill from the maternal breast, would again suck vigorously if placed on it, and concluded that sucking per se could not be considered as a sign of hunger. A few years later (1900) Keller wrote that, since the normal infant sleeps three hours after nursing, although its stomach is empty in two hours, the emptying of the stomach cannot be considered a positive criterion of need for food. Pies, in 1910, considered the reddening and eczema of the lower lip which occurs in undernourished infants as a sign of hunger, and referred it directly to the infant's fruitless sucking. In 1913, Schlossmann concluded from extensive observations on semistarved infants that the sensation of hunger exists only in the imagination.

Meyer and Rosenstern studied the results of starvation in the different types of alimentary disorder, recording particularly the pulse, temperature, respiration and weight changes. Rosenstern later (1911-1912) wrote extensively on the general subjects of hunger and inanition in infancy. These studies are all defective in that they do not distinguish the various factors concerned. Neumann, Pfaundler, Cramer, Süszwein, Barth, and Kasahara have discussed the subject of disturbances in the food urge largely from the point of view of imperfections in the sucking mechanism.

The present studies are concerned particularly with the gastric factors in the urge for food. The major of these, the hunger contractions, was studied by means of apparatus similar to that used by Carlson. A rubber balloon of about 20 c.c. capacity attached to one end of a small soft rubber catheter is inserted into the stomach and inflated, the catheter is attached to a bromoform manometer with a cork float and a writing pennant which records the gastric movements on smoked paper.

The material investigated included five premature infants weighing from 1,200 gm. to 2,500 gm., forty full term new-borns under three weeks of age, and eleven older babies, five between one and two months, two between three and four months, three between four and six months, and one boy of two years with a surgically induced gastric fistula made necessary by the effects of corrosive in the esophagus.

The gastric movements of some of the infants were recorded only once; on others as many as twenty observations were made.

Carlson and Ginsburg refer to the readiness with which most infants accept and retain the tube and balloon. It is naturally impossible to secure a graphic record of the stomach movements of a raging infant. Carlson and Ginsburg did their work on full term new-borns. These infants, as a rule, sleep quietly when not disturbed. The present work was carried on in a dimly lighted, quiet room. I had less difficulty when the infant was left undisturbed in his crib than when I attempted innovations, such as threading a pacifier on the tube or having the infant held in the nurse's arms.

The older babies resent the presence of the tube, and with them it was often necessary to make repeated attempts to secure tracings. Some infants finally became accustomed to the presence of the tube and slept quietly, particularly if the experiments were conducted in the evening. Most of the tracings on the two-year-old boy with the gastric fistula were made when he was awake. The greatest problem was to keep him sufficiently interested to prevent crying and restlessness and at the same time to prevent riotous hilarity. In his case the balloon was introduced directly through the fistula.

It is said that passage of the stomach tube in infants is apt to cause aspiration pneumonia. No ill results followed the procedure carried out in these studies.

Does the presence of the balloon in the stomach act mechanically to produce gastric contractions? Carlson states definitely that it does not, and gives the following reasons for his belief:

> 1. The presence of the distended balloon in the stomach between the contraction periods does not induce these contractions.
> 2. In Mr. V. [his gastric fistula case] the gastric contractions can be observed directly through the large fistula without any balloon in the stomach.
> 3. The contraction periods come on just as frequently without any balloon in the stomach and produce the same effect (hunger).
> 4. In pigeons the periodic strong contractions of the empty crop can be seen directly through the skin, and a balloon in the crop does not alter their frequency or intensity.

The results of this work fully confirm Carlson's and Ginsburg's report that the stomach of the new-born infant exhibits greater hunger contraction than does that of the adult. The intervals between the contraction periods are often less than five minutes and usually not longer than from ten to twenty minutes. The first contraction period after a nursing is apt to consist of from five to twenty separate con-

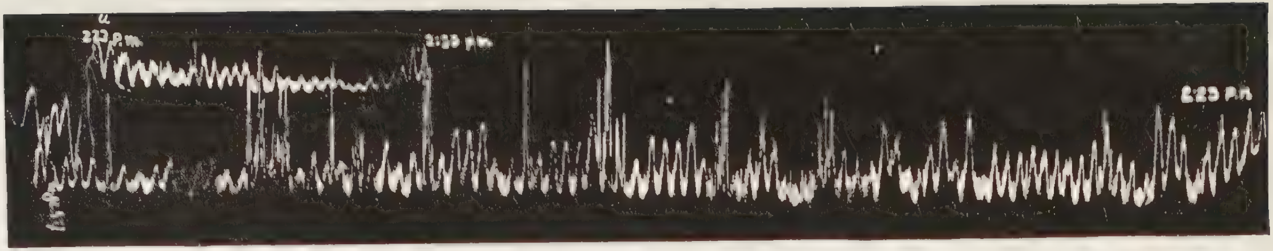

FIG. 1. Hunger contractions in normal, new-born infant. Beginning of partial tetanus at extreme right in lower tracing.

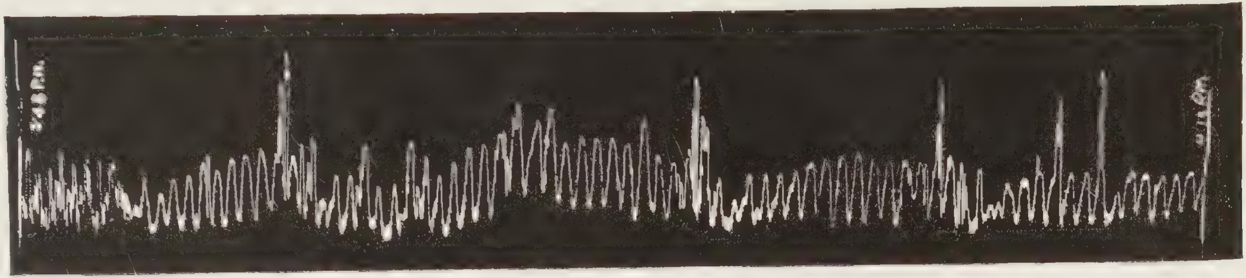

FIG. 2. Prematurely born infant. Typical activity of the premature baby's stomach. Boy F., aged fifteen days; weight, 1,536 gm.; 45 c.c. breast milk six times a day. Previous feeding at 2:30 p. m.

tractions and to last from two to eight minutes. The succeeding contraction periods frequently endure from thirty minutes to an hour or even longer. The duration of each contraction is about twenty seconds. In many of the infants the contraction time of the more powerful contractions, especially in those periods ending in partial tetanus, was about eighteen seconds. Except in the first contraction period after a nursing, endings in partial tetanus were frequently observed. Partial tetanus is sometimes present before the close of the period. With the apparatus used, the force of the single contractions usually sufficed to raise the column of bromoform 2 cm. to 3 cm. During partial tetanus the bromoform may be raised 5 cm.

Patterson found practically continuous hunger contractions in premature pups. It is particularly easy to obtain graphic records of the hunger contractions of the somnolent, prematurely born infant. The stomach of such an infant is in a state of nearly continuous contraction. The individual contractions require about the same length of time for their completion and are as powerful as those of the full term infant. In a tracing begun forty minutes after a feeding of 15 gm. of breast milk to a premature baby (Baby 5) weighing 1,510 gm., the record appears very like that obtained by Rogers from the crop of a pigeon in the second day of starvation. The periods of contraction last two or three minutes, with intervening periods of quiescence of about the same length. The individual contractions last twelve to fifteen seconds and raise the bromoform column 3 cm. to 4 cm. Partial tetanus is frequent. Nine days later, when the infant was receiving more food, in spite of the fact that he had not gained in weight and that the tracing was begun five hours after his last feeding, the record obtained was similar to those from other infants.

Are the hunger contractions more frequent or more powerful in cyanosed infants? May they furnish a stimulus for crying with consequent better aeration of the lungs? In two such cases no significant increase or decrease in the hunger contractions could be observed. No records were taken from any cyanosed premature infants, although such infants are frequently slightly blue for the first few days.

Carlson, working on the adult, was unable to produce hunger contractions by any sort of stimulus acting directly in the mouth or in the stomach, except that he occasionally could, by suddenly distending the stomach, produce a few transitory contractions. He found, uniformly, that the only effect of such local stimulation was inhibitory. In gen-

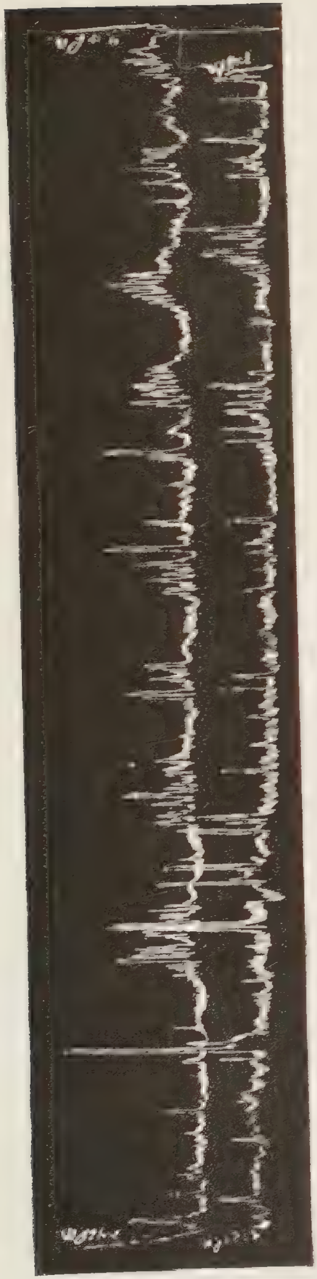

FIG. 3.—Prematurely born infant; shows numerous short, forceful contraction periods. Boy Von, four days old; weight, 1,510 gm.; birth weight, 1,715 gm.; at 2:30 p. m. received 15 c.c. breast milk.

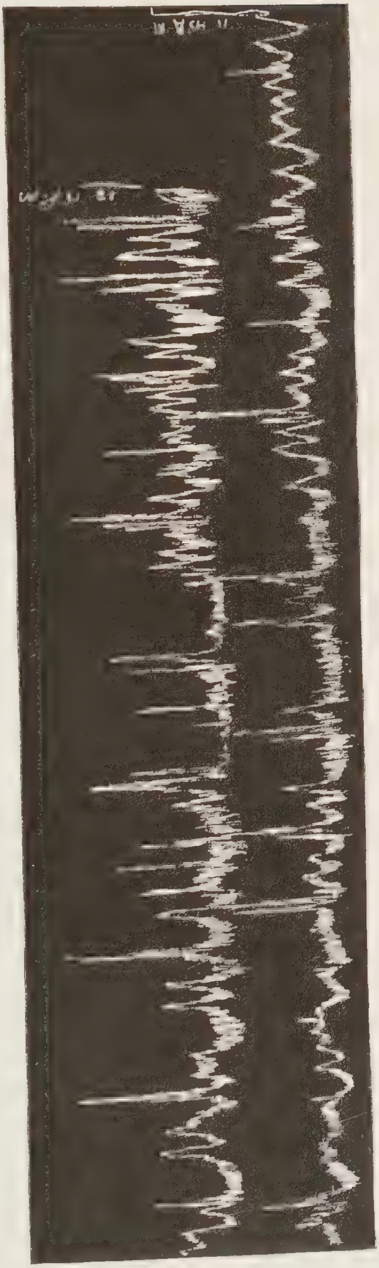

FIG. 4.—Baby Mi., fifteen days old; tracing shows presence of hunger contractions in an infant who nursed poorly.

eral, the taste of salt, sour, bitter, or sweet; or the chewing of agreeable, disagreeable, or indifferent substances, all produce temporary inhibition of the gastric contractions. Chewing palatable foods by the adult when hungry causes an inhibition, made more lasting by the flow of appetite juice in the stomach.

Carlson found that acid and alkaline solutions, food and liquids in the stomach, all inhibit the hunger contractions. Inhibition from the stomach is less transitory than that from the mouth. Boldyreff showed that the periodic contractions of the empty stomach were inhibited by the presence of acid in the intestine. Brunemeier and Carlson completed and enlarged this work. They demonstrated inhibition from the presence of gastric juice or acid chyme in the small intestine. This inhibition from the stomach and intestine is reflex, partly through Auerbach's plexus, but mainly through the long reflex arc with the efferent path to the muscles of the stomach through the splanchnics.

Inhibition from the mouth is not present in the frog (Patterson). Carlson, who suspects that such inhibition involves conscious cerebral processes, has suggested experiments in infants to settle the point.

Repeated trials with breast milk, sugar water, common salt, quinin, and lemon juice in the mouths of premature and new-born infants in my study failed to produce inhibition of hunger contractions.

In general I obtained the same results in an infant of eight weeks. A transitory inhibition occurred occasionally when sugar water was placed in his mouth. In none of the infants did chewing or sucking on the thumb or tube produce inhibition. Nor did such movements or the presence of sugar, breast milk or other substances in the mouth induce hunger contractions.

The boy of two years showed inhibition when sugar or protein milk (his diet at the time) was placed in his mouth. Quinin, dilute hydrochloric acid, small amounts of sugar water, table salt in crystals or solution, did not inhibit. Benzosulphinidum solution inhibited twice. It was not used subsequently. The sight of sugar did not inhibit. He began to cry when he saw his bottle if it was not given to him immediately. Consequently the effect on the hunger contractions of his seeing the bottle could not be registered. During the periods of quiescence the sight of the nurse who fed him did not induce hunger contractions, although he began to whine and tease when she entered the room.

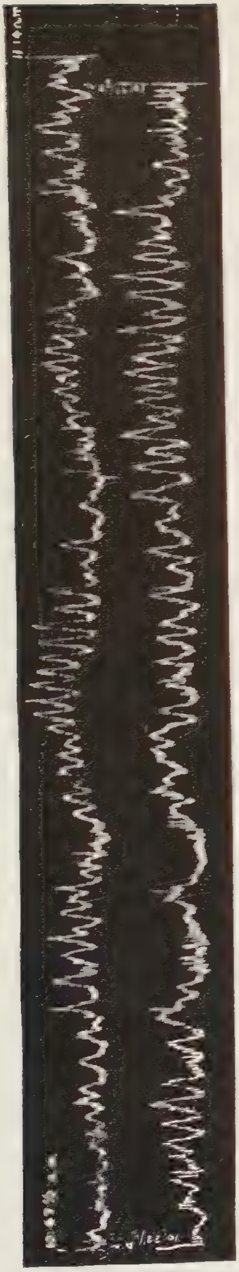

Fig. 5.—Baby Ri., six days old, with congenital myxedema; tracing shows presence of hunger contractions in a babe who nursed poorly

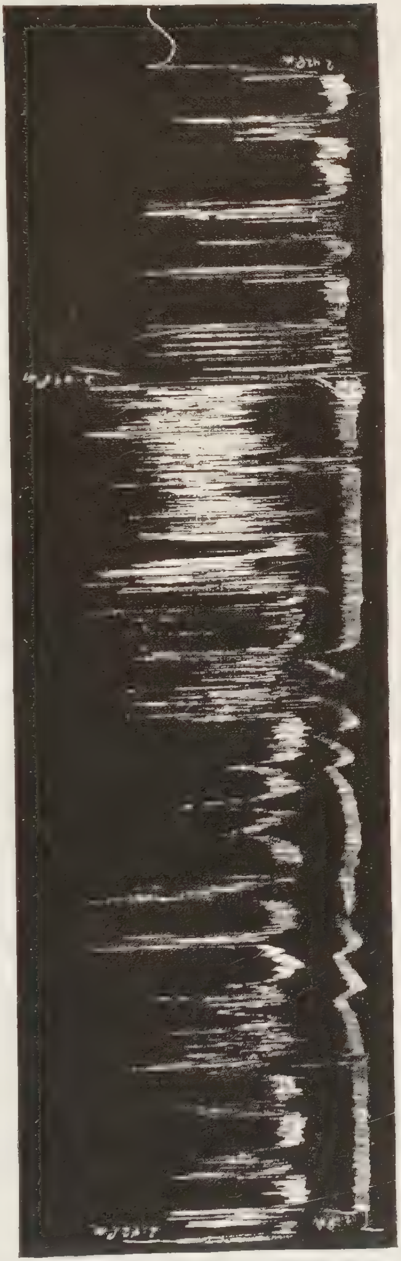

Fig. 6.—Baby J., four months old. Tracing shows development of hunger contractions during the interval following a feeding.

Apparently inhibition from the mouth was produced by those substances only which the child regarded as food. Quinin very evidently made a profound sensory impression, but did not inhibit the contractions. Dilute hydrochloric acid did not inhibit, while unsweetened protein milk (which is slightly sour) did inhibit.

Carlson's hypothesis as to the need of conscious cerebration for the production of inhibitory reflexes from the mouth would appear to offer the correct explanation. It seems to be agreed that the new-born infant leads a subcortical reflex existence (Soltmann-Cramer.) Kussmaul and Thiemich note that the new-born infant accepts sweet and rejects salt, food that is sour and bitter, action which is almost certainly purely reflex on the part of the infant.

My work shows that when 20 c.c. of water or milk are introduced into the stomach during a contraction period inhibition follows invariably. This was found true in infant of all ages. With small amounts of water the inhibition often lasted only three or four minutes, when the contraction period would be resumed.

On the other hand, it was not unusual to recover from 15 cm. to 40 cm. of clotted milk through the stomach tube even an hour after vigorous hunger contractions had begun. This is a considerable portion of the infant's meal, and in these cases would represent from one-sixth to one-fourth of his total intake at the previous feeding. Soltmann showed that the inhibiting nervous mechanism of the heart is much less effectual in the new-born infant than in later life. It seems possible that the nervous apparatus for the inhibition of the gastric hunger movements may likewise be immature. Or the tissue hunger may be so great as to overcome any but the strong inhibition of a heavily laden stomach and duodenum.

The vagi form the sensory pathway from the stomach to the brain. The first reflex centers are the sensory nuclei of the vagi in the medulla. A second center, possibly that for conscious hunger, is located in the optic thalami. Rogers has shown that the picking reflex in the pigeon (analogous to the sucking reflex in the babe) is abolished on removal of the thalami.

The reflex irritability (as indicated by the knee jerk) is increased synchronously with each hunger contraction (Carlson). No observations have been made on the infant's knee jerks during the hunger state; but Zybell has shown that the electrical irritability increases during the first eighteen hours of starvation.

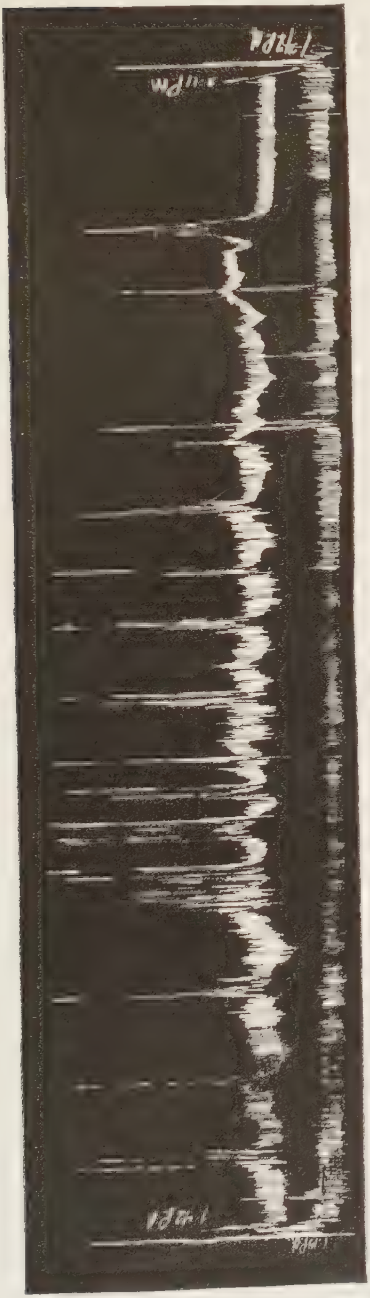

FIG. 7.—Baby J. Tracing similar to that shown in Figure 6.

Let us summarize the events from the close of one meal till the end of the next. The infant sleeps. The upper stomach musculature maintains a tonic grasp on the contained food. The pyloric antrum is traversed by peristaltic waves (Cannon). The stomach gradually empties. The point of origin of the peristaltic waves rises higher and higher. The tonus rhythm of the fundus begins. The stomach empties itself more completely, the tonus rhythm becomes more intense, and the first hunger contractions appear (Rogers and Hardt).

The first contraction period is apt to be short. After a wait of perhaps twenty minutes a longer and more intense hunger period arrives; then another and another. The infant's sleep becomes lighter. He is more easily awakened by external stimuli or by gastric discomfort. He is put to the breast, nurses vigorously, becomes fatigued (Schmidt, Cramer, Pfaundler), or experiences satiety from distention (Neisser and Bräuning) and again goes to sleep.

What constitutes the hunger state? Does it result from the summation of impulses with an increasing psychic and reflex irritability? The evidence is to the contrary. The increase in the reflex excitability is synchronous with the contraction phase of the stomach, and is absent in the intervals between the contractions. In the infant who has been some hours without food the hunger contractions are nearly continuous, and it would be expected that the reflex excitability would be nearly continuously high.

In the absence of hunger contractions the infant often sucks vigorously on the tube attached to the balloon. The receptive mechanism for the institution of the sucking reflex is so delicate that it is impossible to provide, artificially, a minimal stimulus. During the hunger state, when presumably a rapid succession of hunger contractions maintains a low reflex threshold, there may often be observed a succession of automatic sucking movements involving the lips, tongue and lower jaw, each movement providing the necessary stimulus for its successor.

The lay mind is prone to think that the crying infant is hungry. Comby and Czerny and Keller believe that hunger is a minor cause of crying. Rosenstern notes that in hunger young babies are usually quiet, but that the older infants cry more. Schlossmann remarks that the normal infant endures hunger well.

Observations on this point extending over sixteen months of study of the hunger sensation lead me to believe that in normally thriving breast fed infants, except when more than three or four hours have elapsed since the last feeding, neither the hunger contractions themselves nor the increased irritability due to them are ordinarily immediate factors in the production of crying. Young infants sleep throughout strong contraction periods. Older infants often do the same, and are frequently quiet even from twelve to sixteen hours after a feeding. Mental factors produce crying at a very early age. And the fact that crying ceases when food or water is administered may only mean that the infant's attention is diverted to the performance of a pleasurable act.

It may be noted in this connection that the two-year-old boy was happier when allowed to take food into his mouth, and that his outlook on life was much more cheerful on days when he could take nourishment by mouth than on other days when the esophageal constriction increased, and it became necessary to introduce the food through the gastric fistula. This feeding through the fistula was without pain, and the child submitted to it with some pleasure.

What is the time interval between feeding and the first appearance of gastric hunger contractions? Ginsburg, Tumpowsky and Carlson studied this point in thirty normal breast fed infants under four weeks of age. They gave no data as to gain in weight and did not determine the amount of food taken, but stated that the babies nursed till satisfied. They found the average time between nursing and the appearance of hunger contractions to be two hours and forty minutes, with a minimum of two hours and twenty minutes and a maximum of three hours and thirty minutes. My observations on twelve new-born infants under like conditions yielded these results; a minimum of one hour and thirty minutes, a maximum of three hours and thirty minutes, and an average of about two and one-half hours.

Many infants in the first two weeks do not receive a sufficient supply of breast milk. This is particularly apt to be true of the time the babe and the mother remain in the hospital. Consequently, observations made under the conditions so far outlined may be misleading. Table 1 (A, B and C) gives the results of all satisfactory tracings obtained from normally thriving babies on whom sufficient data concerning food intake and weight gain were obtained.

The time required for the development of hunger in the premature infant is noticeably short. In the case of the full term new-borns the figures obtained agree fairly well with those given by Ginsburg, Tumpowsky and Carlson, but are definitely greater than those obtained by me (mentioned in a preceding paragraph) from infants whose food intake was not accurately known.

TABLE 1.—INTERVAL FOR DEVELOPMENT OF HUNGER

A. Premature Infants

Name	Age, days	Food	Feeding interval	Quantity at feeding	Interval before tracing	Time for development of first hunger period	Remarks
Sw.	7	Breast milk	Four hours five times a day	35 c.c.	None	Forty minutes	Premature, Weight 2,140 gm.
Sw.	11	Breast milk	Four hours five times a day	50 c.c.	Twenty minutes	One hour, twenty minutes	Weight 2,240 gm.
Sw.	20	Breast milk	Four hours five times a day	90 c.c.	Fifty-two minutes	Two hours	Weight 2,470 gm.
Sw.	25	Breast milk	Four hours five times a day	75 gm.	Thirty-eight minutes	One hour, fifty minutes	Weight 2,565 gm.
St.	13	Breast milk	Four hours five times a day	30 c.c.	None	One hour	Premature, Weight 2,270 gm.
St.	14	Breast milk	Four hours five times a day	50 c.c.	None	Forty minutes	Weight 2,280 gm.
St.	25	Breast milk	Four hours five times a day	90 c.c.	One hour, thirteen minutes	One hour, fifteen minutes	Weight 2,450 gm.
St.	28	Breast milk	Four hours five times a day	90 c.c.	Thirty-eight minutes	One hour	Weight
St.	36	Breast milk	Four hours five times a day	100 c.c.	Thirty-two minutes	One hour, fifty minutes	Weight 2,720 gm.
Fre.	9	Breast milk	Four hours six times a day	45 c.c.	One hour, thirty-eight minutes	One hour, thirty-eight minutes	Premature, Weight 1,380 gm.
Fre.	15	Breast milk	Four hours six times a day	45 c.c.	One hour, eighteen minutes	One hour, eighteen minutes	Weight 1,530 gm.
Fre.	16	Breast milk	Four hours six times a day	45 c.c.	Twenty-three minutes	One hour, fifteen minutes	Weight 1,535 gm.
Fre.	21	Breast milk	Four hours six times a day	65 c.c.	Two hours	Two hours, twenty minutes	Weight 1,710 gm.

B. Full Term New-born Infants

H.	8	Breast milk	Four hours five times a day	?	One hour, twenty-two minutes	Three hours, fifty minutes	Weight 3,590 gm.; gain in four days 90 gm.
Dav.	8	Breast milk	Three hours eight times a day	75 gm	One hour, fifty-five minutes	Two hours, twenty five minutes	Weight 4,160 gm.; gain in five days 260 gm.; 10 c.c. of milk clot removed from stomach one hour after beginning of hunger contractions.
Dav.	9	Breast milk	Four hours (for preceding twenty-four hours) five times a day	?	Two hours, thirty minutes	Two hours, thirty minutes	Weight 4,200 gm.; gain in six days, 300 gm.; ½ c.c. thick mucus removed from stomach one-half hour after beginning of hunger contractions.
Wes.	8	Breast milk	Four hours five times a day	100 gm.	One hour, thirty minutes	Three hours, ten minutes	Fourteen hours fast previous to last feeding.
A.	9	Breast milk + cow's milk } aa 8 % lactose	Three hours eight times a day	70 gm.	One hour, forty-five minutes	Two hours, ten minutes	Weight 3,610 gm.; gain in six days 230 gm.; 20 c.c. of thick soft milk clot removed from stomach fifty minutes after beginning of hunger contractions.
A.	10	Breast milk + cow's milk } aa 8 % lactose	.	70 gm.	One hour, fifty-two minutes	Two hours	15 c.c. of fluid and curds removed from stomach thirty minutes after beginning of hunger contractions.
Wal.	10	Breast milk	Four hours five times a day	95 gm.	One hour, thirty minutes	Four hours	Weight 3,240 gm.; gain in six days, 260 gm.
D.	12	Breast milk	Four hours five times a day	115 gm.	Two hours, thirty minutes	Two hours, thirty minutes	Weight 3,720 gm.; gain in seven days, 400 gm.

Table 1.—Interval for Development of Hunger.—(*Continued*)

C. Normal Infants Over Two Weeks of Age

Name	Age, days	Food	Feeding interval	Quantity at feeding	Interval before tracing	Time for development of first hunger period	Remarks
Gor.	18	Breast milk	Four hours five times a day	85 gm.	Two hours, twenty-three minutes	Four hours	Weight 3,500 gm.; gain in thirteen days, 70 gm.
Gor.	19	Breast milk	Four hours five times a day	110 gm.	One hour, fifty-eight minutes	Three hours, twenty-five minutes	
Way.	Months 3.5	Buttermilk + flour + saccharose	Four hours five times a day	150 c c	Two hours, twenty-seven minutes	Three hours, twelve minutes	Weight 4,960 gm.; gain in seven days, 440 gm.
Way.	3.5	Buttermilk + flour + saccharose	Four hours five times a day	150 c.c.	Fifty-seven minutes	Three hours, twenty minutes	40 c.c. of thick white material removed from stomach twenty minutes after beginning of contraction period.
Way.	3.5	Buttermilk + flour + saccharose	Four hours five times a day	150 c'c.	Two hours, three minutes	Four hours, thirty-five minutes	
Herm	4	Breast milk	Two or three hours irregular	?	Two hours, forty-five minutes	Three hours, thirty minutes	Well nourished; gaining in weight; normal baby; cared for at home; not in hospital
J.	4	Breast milk	Five times a day	?	Two hours, fifteen minutes	Three hours, thirty minutes	Well nourished; gaining in weight; normal baby; cared for at home; not in hospital.
Ad	4	Malt soup	Four hours five times a day	125 c.c.	Two hours, thirty-seven minutes	Three hours, thirty minutes	Weight 3,500 gm.; gain in two weeks, 200 gm.; prematurely born; 1,600 gm. at birth.

The time required for the development of hunger in any one infant is fairly constant over a short period of time, provided the amount and kind of food is not changed. This conclusion rests not only on the results shown in Table 1, but on a dozen other observations on infants whose feeding conditions remained constant during the time in which studies were made.

With the older infants difficulty in maintaining quiet, after the insertion of tube and balloon, limits the number of observations which give positive evidence of the first appearance of hunger contractions. Many less successful observations on healthy, normally developing infants yield this negative evidence that in such infants more than one month of age I did not observe the development of hunger before the end of three hours.

It should be noted further that the contraction period, the first appearance of which is recorded in Table 1, is the first one to develop after feeding. This period is usually short and is not made up of forceful contractions. With Infants J. and A. more intense and more nearly continuous contractions did not begin for four and four and one half hours, respectively.

Habits as to feeding interval affect the time required for the development of hunger chiefly as they influence the emptying time of the stomach. It has been shown that the speed of gastric emptying is proportional to the length of time during which the individual has been without food (Tobler, Haudek and Stigler), and that large feedings are emptied with relatively greater rapidity than small ones (Tobler and Bogen). Habits undoubtedly exert a more powerful influence on the mental factors associated with appetite than on hunger itself.

Tables 2, 3 and 4 illustrate the shorter time required for the development of hunger in infants with chronic nourishment disturbance, and indicate that the presence of hunger contractions is not in itself evidence that the stomach is ready for food.

In the columns headed "Remarks" in Tables 1, 2, 3 and 4, are notes on material recovered with the stomach tube after the onset of gastric hunger contractions. In normal babies, however, there probably does exist a relation between the emptying time of the stomach and the interval for the development of hunger.

Observations on the emptying time in infants, so far reported, have been made either with the relatively stiff catheter, the stomach tube, or the roentgen ray. The flexible tube introduced by Rehfuss should

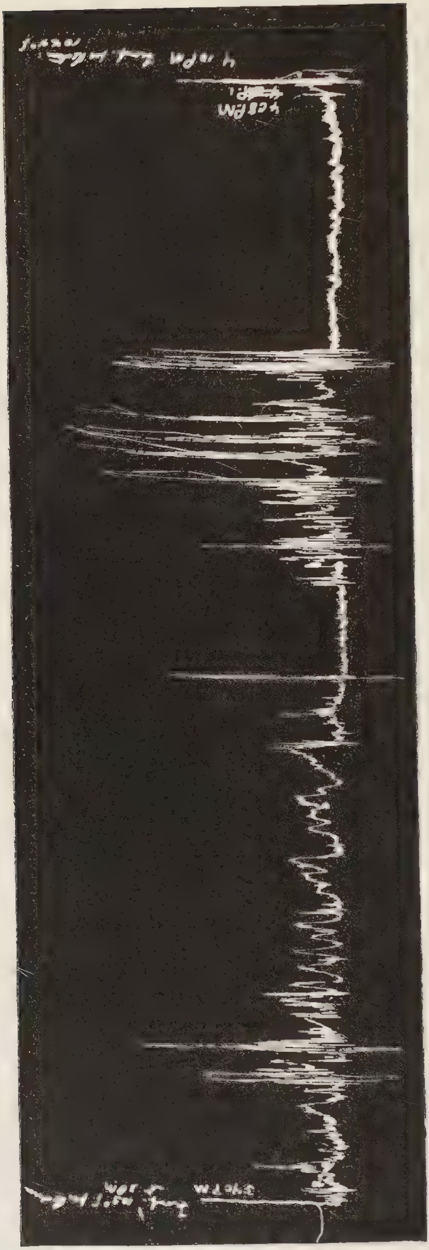

FIG. 8. N. N., a two-year-old boy with typhoid fever. Hunger contractions present when rectal temperature ranged between 104.4° and 105°F.

replace the catheter for this purpose; it was used in my work. The literature does not contain reports of the time required for gastric digestion in the premature infant. The emptying time in normal breast-fed infants under one week is usually less than one hour (Leo). The roentgen-ray observations of Ladd and of Tobler and Bogen would indicate that in normal breast-fed infants the stomach is frequently not empty until after two to three hours. The figures obtained with the use of the stomach tube by Epstein, Czerny, Keller and Cassel indicate a delayed emptying time in gastro-intestinal disease.

Table 2.—Hunger in Atrophy Resulting from Continued Starvation

N. N., aged two years; gastric fistula; weight fluctuating between 6,800 gm. and 7,200 gm.; typhoid fever December 1 until December 14, 1916.

Date 1916	Food	Time of last feeding	Beginning of tracing	Remarks
10/19	Diluted cow's milk + general diet	6 a. m.	10:15 a. m.	Practically continuous hunger periods until 10:50 a. m.
10/20	Diluted cow's milk + general diet	10 a. m.	2:12 p. m.	Practically continuous hunger periods until 3:15 p. m.
11/1	....	10 a. m.	2:16 p. m.	One hunger period at 2:45 p.m. to 2:50 p. m. Hunger contractions practically continuous after 3 p. m. until 4:50 p. m.
11/10	160 c.c. cow's milk at preceding feeding	2 p. m.	2:45 p. m.	Observations continued until 5:10 p. m. No hunger periods, but child cried or was restless over half of the time.
10/11	160 c.c. cow's milk at preceding feeding	2 p. m.	9:00 p. m.	Practically continuous contractions until 11 p. m.
11/11	200 c.c. protein milk + 7 per cent dextrimaltose	5 p. m.	10:12 p. m.	Practically continuous contractions until 11 p. m.
11/12	200 c.c. protein milk + 7 per cent dextrimaltose	5 p. m.	8:41 p. m.	First hunger period at 9:30; practically continuous from 9:45 on until 10:44 p. m.
11/29	200 c.c. protein milk + 7 per cent dextrimaltose	1 p. m.	4:02 p. m.	First hunger period began at 4:35 p. m.; practically continuous from 5 p. m. on until 5:42 p. m.
12/27	200 c.c. protein milk + 7 per cent dextrimaltose + cereals	9 a. m.	12:34 p. m.	Hunger periods practically continuous until 1:30 p. m.
12/28	200 c.c. protein milk + 7 per cent dextrimaltose + cereals	9 a. m.	12:22 p. m.	Hunger periods began about 12:50; hunger periods became continuous after 1:20 p. m.
12/30	200 c.c. protein milk + 7 per cent dextrimaltose + cereals	5 a. m.	10:13 a. m.	Practically continuous hunger periods until 11:20 a. m.

Major, using the roentgen ray, finds the emptying time delayed in dyspepsia, but accelerated in decomposition. With the same method Pisek and LeWald found the emptying time to be shorter in infants

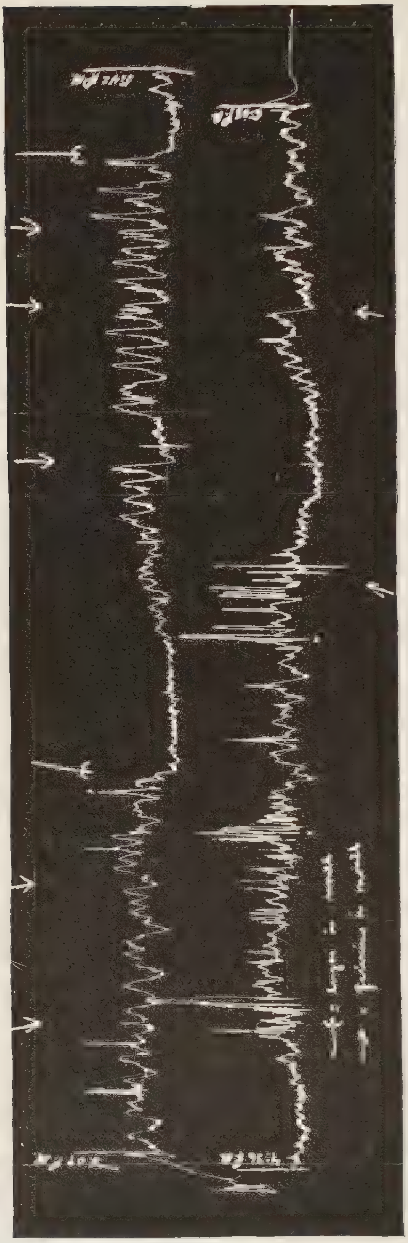

FIG. 9.—N. N., two years old. Tracing shows inhibition from sugar in the mouth; absence of inhibition from quinin in the mouth.

with chronic disturbances of nutrition. These last findings, taken in conjunction with the already quoted reports of Tobler, and of Haudek and Stigler, that the emptying time is shortened by hunger, are suggestive of the results here obtained experimentally; that is, the greater gastric hunger contraction in infants with chronic nourishment disturbance.

Not only is the interval for development of hunger shorter in such infants, but the contractions become much more intense. November 10, 1916, the two-year-old boy (Table 2), whose weight in spite of a calorically sufficient intake had remained stationary, and whose temperature had been irregular, developed fever and diarrhea. After eight hours of starvation, with temperature normal, the graphic record of his gastric activities resembled those of the starving pigeon and of the premature infant already mentioned. The contractions were continuous and required only twelve seconds for their completion. Next day the child was put on protein milk and thereafter improved.

Table 3.—Hunger in Exudate Diathesis

Aus., 7 weeks old, Dec. 19, 1916. Feeding interval 4 hours, 5 times a day.

Date	Weight, gm.	Food: breast milk + buttermilk + flour + saccharose, c.c.	Time of last feeding	Beginning of tracing	Remarks
12/19/16	4,450	100	1 p. m.	3:28 p. m.	Hunger contractions began at 3:30 p. m. Hunger contractions continuous from 3:55 to 4:37 p. m.
12/22/16	4,460	100	9 a. m.	11:49 a. m.	Hunger contractions present at 11:49 a. m. Hunger contractions continuous until 12:50 p. m.
12/22/16	4,460	150	1:15 p. m.	3:34 p. m.	Hunger contractions began at 5:45 p. m.
1/ 6/17	4,640	125	8 a. m.	10:55 a. m.	Hunger contractions began at 10:55 a. m. Hunger contractions continuous until 12:21 p. m.
1/ 8/17	4,640	125	8:40 a. m.	11:51 a. m.	Hunger contractions began at 12 m. Hunger contractions strong and continuous after 12:18. Babe was restless.
1/11/17	4,650	125	8:45 a. m.	11:11 a. m.	Hunger contractions present by 11:45 a. m. Hunger contractions continuous until 1:35 p. m.
1/13/17	4,740	150	8:20 a. m.	11:03 a. m.	Hunger contractions began at 11:45 a. m. Hunger contractions continuous from 12 to 1 p. m.
1/15/17	4,770	150	8:45 a. m.	11:01 a. m.	Hunger contractions present at 11:20 a. m. Hunger contractions continuous from 11:30 a. m. until 12:50 p. m.
1/15/17	4,770	150	12:50 p. m.	3:21 p. m.	Babe cried a large part of time; no evidence of hunger periods until 5 p. m.

It is generally agreed that mixtures with high fat content leave the stomach most slowly, while those with low fat and high carbohydrate leave most rapidly. In Infants A. and W. the time interval for the development of hunger contractions was much longer when they received low fat and high carbohydrate, and shorter when they received high fat and low carbohydrate. This would be paradoxical if the gastric hunger contractions depended exclusively on the emptying time. It is, then, only in normal babies, receiving well tolerated food in sufficient quantity, that the development of hunger waits on the emptying of the stomach.

The interval necessary for the development of hunger depends in part on the form of nourishment and is shortest with that food which least satisfies the infant's tissue need (Table 4). The question as to whether the rapid development of hunger in qualitatively poorly nourished infants depends on the administration of food deficient in carbohydrate in particular, or on the giving of food poorly tolerated in general, is not answered. Records of the gastric contractions in infants suffering from the chronic nourishment disturbance due to long continued carbohydrate overfeeding (the "Mehlnährschaden" of Czerny) would help to settle this point.

Attention has already been called to the heightened electrical reactions found by Zybell in hungry infants. I also wish to mention the findings of Finkelstein, Thiemich and Japha that the electrical irritability is frequently heightened in artificially fed infants, and of Czerny and Moser that there is an increase in the electrical irritability of infants suffering with "Mehlnährschaden." It is possible that the heightened electrical irritability in all depends on the increased hunger contractions due again in part to the constant chemical stimulation reaching the stomach from the semistarved tissues.

Most premature infants and many young infants nurse poorly. The consequent effect on lactation and on the babe's nourishment is serious. An extensive literature on this subject has been developed in German, but there is surprisingly little in French and in English.

In 1888, Auerbach described the infantile manner of sucking, which depends on the chewing muscles, and Escherich showed its teleologic importance. The reflex paths and center in the medulla were demonstrated in 1894 (Basch). Cramer, Suszwein, Finklestein, Rott, Rosenstern, Barth and Kasahara have further studied the question and report results which in general support the theory that the inability to

TABLE 4.—INTERVAL FOR DEVELOPMENT OF HUNGER IN INFANTS WITH CHRONIC DISTURBANCE OF NUTRITION AND SHOWING INFLUENCE OF CHANGE IN FORM OF NOURISHMENT

Name and date	Age, month	Diagnosis	Weight, gm.	Food	Interval before tracing	Time for development of first hunger period	Remarks
Til.	3	Atrophy	Stationary 4,080	120 gm. protein milk + 7 per cent dextrimaltose 5 times a day.	. . . .	. . . . . .	Hunger periods with partial tetanus less than three hours after feeding.
Ad. 2/26/17	4	Chronic alimentary disorder due to overfeeding with milk.	3,300	150 c.c. ½ milk + 10 per cent saccharose 5 times a day			Hunger contractions present in two hours and twenty minutes.
Ad. 3/ 8/17	4	Chronic alimentary disorder due to overfeeding with milk.	3,500	125 c.c. malt soup 5 times a day.			Babe improved clinically; hunger contractions first appear in three and one-half hours.
Way.	3	Chronic nourishment disturbance with eczema.		Mixture containing 8 per cent fat. Feeding intervals short and irregular. After entrance to hospital fed 5 times a day.			Entered hospital April 14, 1917.
4/14/17	..	....	4,200	150 c.c. ½ cow's milk + 10 per cent saccharose.	Two hours, seven minutes	Two hours, seven minutes	Stomach emptied three hours after feeding; 0.5 c.c. of mucus and thick curd obtained.
4/23/17	..		4,510	150 c.c. ½ cow's milk + 10 per cent saccharose.	Two hours, ten minutes	Two hours, ten minutes	Eczema increased; 40 c.c. of clotted milk and clear thin fluid recovered from stomach three hours and twenty-five minutes after feeding.
5/ 1/17	..	....	4,960	150 c.c. buttermilk + flour + saccharose.	Two hours, three minutes	Four hours, thirty-five minutes	Eczema has disappeared.
5/ 2/17	..	....	4,960	150 c.c. buttermilk + flour + saccharose.	Two hours, twenty-seven minutes	Three hours, twelve minutes	
5/ 3/17	..	....	4,960	150 c.c. buttermilk + flour + saccharose.	Fifty-seven minutes	Three hours, twenty minutes	40 c.c. of thick white material removed from stomach twenty minutes after beginning of first contraction period.

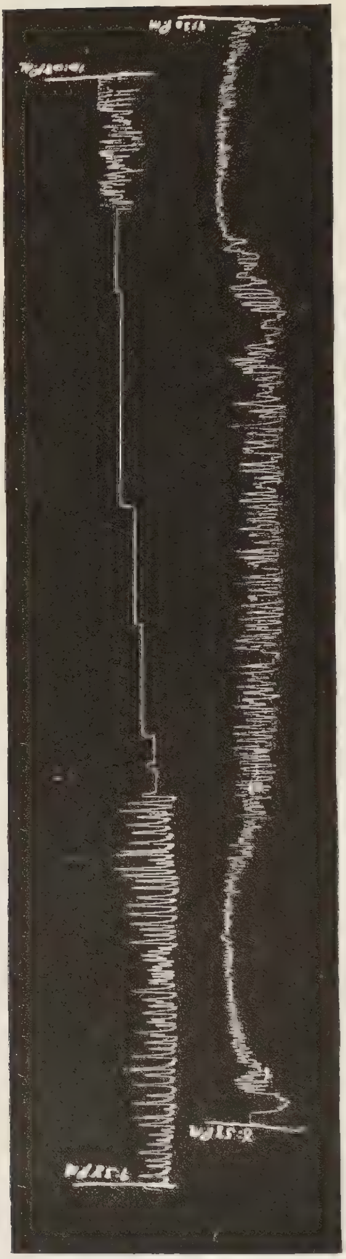

FIG. 10.—N. N. (Fig. 9.). The tracing shows continuous short contractions in atrophy after eight hours of starvation.

nurse well is to be attributed primarily to an imperfect nervous mechanism and not to muscular weakness.

For further elucidation of the question, tracings of the movements of the empty stomach were taken in two infants who were extreme examples.

The first baby (Baby M.), weighing 2,700 gm. at birth and presenting no anatomic peculiarities, took very little from the mother's breast during the first three weeks, although sufficient milk was expressed therefrom to feed the baby and to complement the feedings of other babies.

The second infant (Baby T.), aged three months, had weaned himself from the breast, had developed dyspepsia and atrophy on artificial feeding, and could be made to take his food from the bottle only with great difficulty. He seemed able to fix his attention on anything other than the act of feeding. In these infants as well as in the five prematures, and in one typical case of congenital myxedema, hunger contractions of at least normal force and duration were present. At the time they were studied, none of the infants was able to nurse successfully. In all, the sucking reflex was qualitatively present.

This study does not solve the problem of the causation of feeble nursing, but does limit the field of possibilities by excluding derangements of the primitive hunger apparatus.

Carlson reports Rupp's finding that hunger contractions persist during the fever excited by the administration of typhoid vaccine. The boy with the gastric fistula contracted typhoid fever from a carrier. Tracings taken while his rectal temperature ranged between 104.4°F. and 105°F., show the presence of hunger contractions.

Carlson and Ginsburg found hypertonicity and hypermotility in the stomachs of two infants with pylorospasm and stenosis. From a six weeks' old infant (Baby S.) with pyloric stenosis, I obtained records which agree with Carlson and Ginsburg's description of periods of tetanus lasting several minutes interspersed with vigorous contractions of normal duration.

Carlson suggests that pylorospasm and stenosis may be an expression of gastric hypermotility. His cases were seen late, as was the one here reported. In the absence of tracings taken at the beginning of the disease, it is likely that the hypermotility results from the inanition following the obstruction at the pylorus. And without definite knowledge that the stomach was washed empty, the long periods of tetanus observed may represent the so-called visible gastric peristalsis.

SUMMARY

The study of fifty-six infants ranging from birth to two years of age gave the following results:

1. Confirmation of previous work, that hunger contractions are greater in the new-born infant, with description of these contractions.

2. Determination of the still greater hunger contraction in the stomachs of prematurely born infants, with description of these contractions.

3. There is no relation between cyanosis and hunger contractions.

4. Inhibition of the hunger contractions from the mouth does not occur in young infants.

5. Inhibition of the hunger contractions from the mouth in older infants is present only as the result of stimuli, which the babe has learned to recognize as food. It does not occur with substances producing equally strong sensory impressions, but which are not considered by the infant as food.

6. Inhibition from the mouth is psychic in character.

7. Reflex inhibition from the presence of food in the stomach is present in infants of all ages.

8. This reflex inhibition from the stomach may be only partially developed in young infants.

9. Successive automatic sucking movements—each sucking act serving as the stimulus for its successor—are present during the hunger state, when the reflex threshold is kept almost constantly low by a rapid succession of hunger contractions.

10. In normally developing breast fed babes, hunger is not ordinarily an immediate cause of crying.

11. The average time required for the development of hunger in healthy infants gaining in weight and receiving a known sufficient amount of food is, in prematures, under one month, one hour and forty minutes, with a maximum of two hours and twenty minutes and a minimum of forty minutes; in full term infants under two weeks, two hours and fifty minutes, with a maximum of four hours and a minimum of two hours; in infants from two weeks to four months, three hours and forty minutes, with a maximum of four hours and thirty-five minutes and a minimum of three hours and twelve minutes (Table 1).

12. The time required for the development of hunger in any one

infant is fairly constant over a short period of time provided the amount and kind of food is not changed (Tables 1, 2, 3 and 4).

13. The time required for the development of hunger in infants with chronic nourishment disturbance is shorter than in normal infants (Tables 2, 3 and 4).

14. The time required for the development of hunger is shorter when the infant receives food which is poorly tolerated (Table 4).

15. Hunger contractions occur in these infants long before the stomach has emptied. Consequently their presence is not in itself an indication that the stomach is ready for food.

16. The feeble nursing exhibited by most prematures and by many older infants is not due to derangement of the primitive hunger apparatus. Hunger contractions are present and of normal intensity in such infants.

17. Hunger contractions were present in one infant with congenital myxedema.

18. Hunger contractions were present in a two-year-old boy with typhoid fever when the rectal temperature ranged between 104.4° F. and 105° F.

19. Confirmation of previous findings of increased hunger contractions in infants with pyloric stenosis.

SOME CLINICAL AND EXPERIMENTAL OBSERVATIONS ON GASTRIC ACIDITY USE OF THE GAS-CHAIN METHOD*

GOLDER L. McWHORTER

In order to determine the effect produced by chronic inflammatory and altered physiologic changes in the gastro-intestinal tract, I have undertaken the study of the gastric secretion in such conditions by means of the exact gas-chain method of determining the acidity, and have plotted curves, comparing the results with those gained by the titration method. Previous to this time acidity curves have been made clinically only by the titration method. My estimations were made from specimens collected at short intervals after test meals in clinical cases and in animal experiments. In order to obtain pure juice in the latter experiments Pawlow pouches were made and estimations of secretion carried on before and after the production of lesions or altered physiologic conditions. In such surgical conditions there may be an increased acidity in the gastric contents; in these observations I have attempted to determine whether such an increase is due to an actual increased acidity in the gastric juice.

The apparatus used in the gas-chain method of determining the hydrogen ion concentration was put at my disposal by McClendon. This apparatus consists of a hydrogen electrode, a calomel electrode and a potentiometer for measuring electromotive force. The principle of the gas-chain method is well described by Sedgwick. As to the colorimetric determination of the hydrogen ion concentration the results so far, when applied to gastric contents containing varying amounts of protein and salts, have proved inaccurate and unavailable for following changes in reaction during digestion.

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The bibliography is herewith omitted.

A solution is acid in reaction when it contains an excess of hydrogen over hydroxyl ions, neutral when they are in equal numbers and alkaline when hydroxyl ions predominate. Pure distilled water dissociates into hydrogen and hydroxyl ions, the extent of the dissociation being such that in one liter of water at 22°C. there is approximately $^1/_{10000000}$ gram of hydrogen ions; that is, concentration of the hydrogen ions is $^1/_{10000000}$ normal (atomic weight of hydrogen as 1). The shorter method of representing so many figures is usually adopted, the logarithmic notation: thus, $^1/_{10000000}$ H. Acid $= 10^{-7}$or simply pH 7. Since there is one hydroxyl ion formed for each hydrogen ion the concentration of the hydroxyl ions must also equal pH 7.

The measurement of the pure gastric juice has been made by Menten, and found to vary from pH = 0.92 to 1.58, highest in the appetite juice and lowest in the secretion in the empty stomach. Michaelis and Davidsohn state that the average acidity of the stomach contents after an Ewald test meal means 0.028 to 0.0015; hyperacidity, 0.011 to 0.088; hypoacidity, 0.000,0041 to 0.000,0001. McClendon, after normal meals, found a rise in acidity for two or three hours, when it remained constant until the food had left the stomach. Carlson believes that the view of Pawlow that gastric juice is secreted at uniform and constant acidity is true for man only in regard to the appetite, digestive and hunger juice secreted at a fairly high rate, and has observed that the normal gastric mucosa is capable of secreting a juice of submaximal acidity. Hardt after experimental production of gastric and duodenal ulcers found no increased acidity. Grey after cholecystogastrostomy found no change in the acidity of the gastric secretions.

Pawlow believes that the slower rate of secretion may give a chance for the HCl acid to be partly neutralized by the mucus in the stomach. Boldyreff has shown the entrance of the intestinal contents to be the most important factor in neutralization of the stomach contents

For the purpose of comparison of acidity estimations a standard test meal was adopted which consisted of two slices of bread with crusts removed and two glasses of distilled water. In all estimations the Rehfuss tube was used for collecting specimens. Collections were made every fifteen minutes from the time the test meal was eaten until no more material could be aspirated. Unfiltered gastric juice was used in the estimations, though at times it was strained

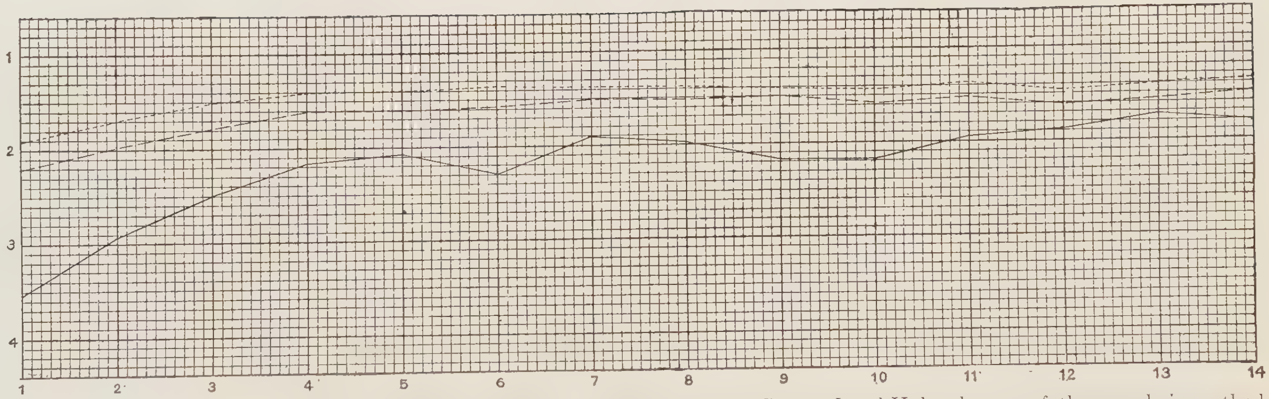

Fig. 11.– The lower solid line is a composite of thirty-two acidity curves in Groups I and II by the use of the gas-chain method of determining the pH. The broken line represents a composite curve of the pH derived from the dimethyl amino azobenzene acidity, assuming it to be pure HCl. The dotted line in the same way represents the phenolphthalein acidity. The estimations were made from specimens collected at fifteen-minute intervals.

through coarse gauze. In order to compare the actual acidity to the acidity obtained by the usual titration methods, samples of the juice were titrated against a $\frac{N}{50}$ KOH solution, using dimethyl amino azobenzene and phenolphthalein as indicators. I have found that the value of these indicators used clinically in determining free and total acidity by titration with an alkali is in many cases parallel, though not equivalent, to the actual acidity as determined by the gas-chain method (Fig. 11). Much discussion has arisen as regards the value of the titration methods; consequently, I have made observations by both methods, and have plotted, also, corresponding curves to compare the values of the dimethyl amino azobenzene acidity to the actual acidity. Figure 11 shows the curves running fairly constantly parallel throughout; however, the acidity as determined by the "indicator method" is uniformly higher than the actual acidity. Figure 12 shows the plate for determining the hydrogen ion concentration from the dimethyl and phenolphthalein acidity as determined with the above indicators. This assumes the acidity to be in terms of pure HCl acid, which dissociates, as shown by the curve. Fraenkel found the Congo-red acidity to be almost constantly parallel to the actual acidity as determined by the gas-chain method, and states that the phenolphthalein acidity does not show the free HCl acid even in the pure gastric juice.

The plotted curve of acidity of thirty-seven cases may be divided into several phases for study: (1) the ascension, usually the first hour, indicating the rapidity and intensity to a known stimulus; (2) the high point or acme, to note whether accelerated or retarded and whether abrupt or sustained; and (3) the period of descent or decline and the possible secondary rise, also to note the character and modification of the food residues. The cases observed include chronic appendix and gall-bladder cases before and after operation, hernia, carcinoma of the stomach, kidney stone, huge ovarian cyst, gastrojejunostomy, duodenal ulcer, prostatic hypertrophy and a few remote surgical conditions.

In Group I, ten of thirteen cases tend to a gradual rise, and at the end of the first hour have reached the maximum from which they usually decline gradually. Three cases have a delayed rise. The average time juice could be obtained was two and a half hours, food being absent in the last fifteen minutes to three-quarters of an hour.

In Group II the curve either remains continuously high, or after a fall, undergoes a second rise, often higher than the primary one, near or at the end of digestion. In this first subdivision are six cases, two of which have a delayed rise; in the second subdivision are twelve cases, one having a delayed rise. The average time specimens could be obtained in the first division of Group II was two hours; in the second, two and three-quarter hours; in one-half of these cases food was present to the end.

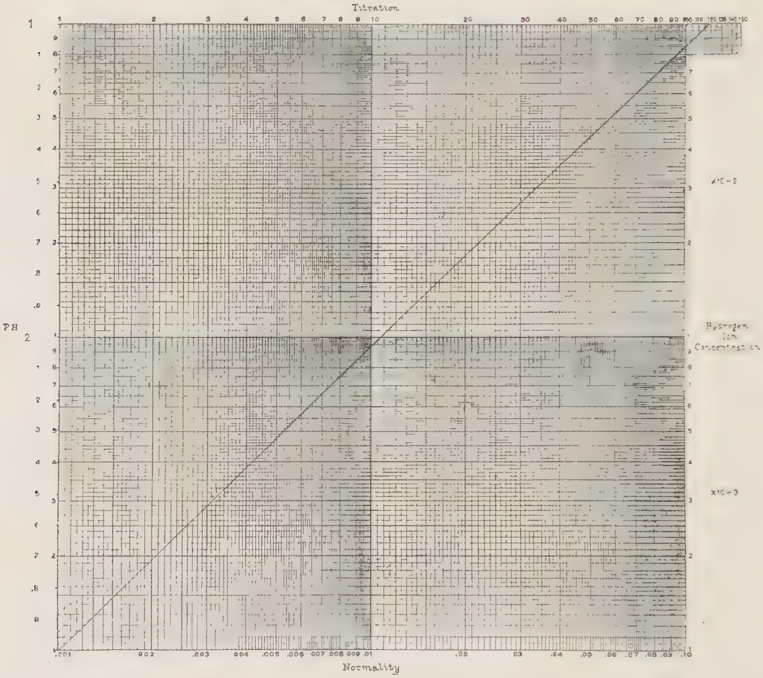

FIG. 12.—By this chart the degree of dissociation of HCl at different degrees of strength may be determined and either the hydrogen ion concentration or the pH estimated. The curve continued from 120 c.c. N/10 HCl = pH 1 would show the dissociation of HCl at higher concentrations. 130 c.c. N/10 HCl = pH 0.996; 140 c.c. N/10 HCl = pH 0.993; 150 c.c. N/10 HCl = pH 0.9. (Chart plotted for me by J. F. McClendon.)

In Group III, I have placed five cases of hypoacidity in which the acidity was less than pH = 4. Michaelis and Davidsohn place hypoacidity between 0.000,41 and 0.000,000,1. Considerable peptic digestion takes place at pH = 4 and very rapid digestion at pH = 0.78 (Sorensen[1]), so that digestion is retarded but not stopped until

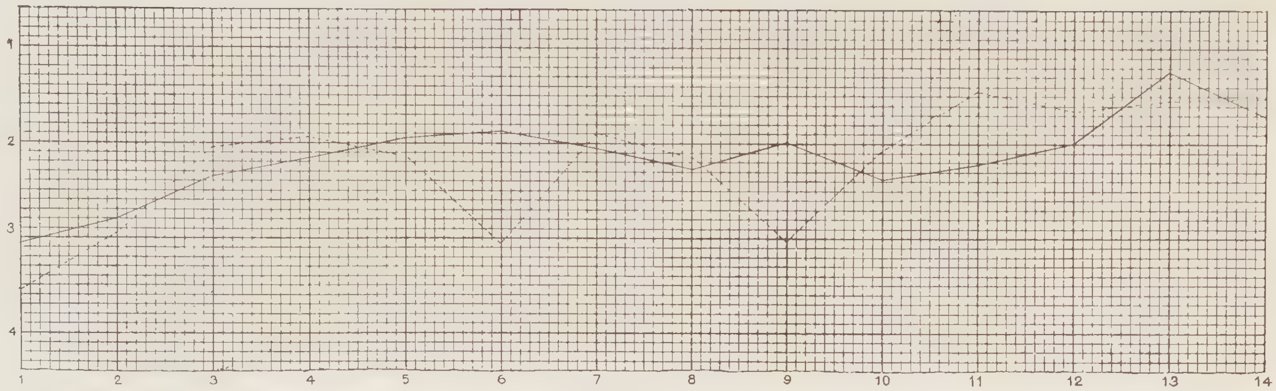

Fig. 13. The solid line represents a composite of eight acidity curves in chronic appendicitis. The broken line represents a composite of the gall-bladder acidity curves. Both of the acidity curves are in terms of pH as determined by the gas-chain method. The estimations were made from specimens collected at fifteen-minute intervals.

acidity is less than pH = 4. Dimethyl amino azobenzene does not react to an acidity less than about a pH of 4. In one of these cases the curve of acidity later, after removal of a gall-bladder with stones, rose to a normal acidity curve. The average time specimens could be obtained in this group was two and three-quarter hours.

Hypersecretion was demonstrated in gastric ulcer cases thirty years ago (Rubow). Recently it has been found not only in inflammatory conditions of the gall-bladder, appendix and in pelvic and other organs but in normal individuals. The vagus is considered one factor in producing this condition.

The values of pH before operation were taken in eight cases with chronic appendicitis and a composite curve plotted (Fig. 13). The curve gradually rises to the end of the first one and a half hours, then falls slightly to the two-and-a-half-hour period, when it begins a secondary rise higher than the digestive rise, lasting to the end of collection. Two of these cases, having definite gastric disturbances, had early high acidity with an exaggerated secondary rise. Secretion in these chronic appendix cases was obtained for an average of two and three-quarter hours, but was obtained longer in the two cases with definite gastric symptoms. Food was present in three cases without symptoms to the end of observation, but in the others it was absent in the last three-quarters of an hour.

In addition to cases studied by the fractional method I ran a series of fourteen clinical cases, comparing the secretion obtained one hour after an Ewald meal before and after operation for chronic appendicitis. I estimated the titration acidity in all of these cases, the total chlorides in five and determined the pH in nine cases. There was some variation in the pH but no constant change after operation; therefore these results are not tabulated.

A composite curve of seven cases of gall-bladder disease was plotted (Fig. 13). On account of variations in the individual acidity an irregular curve was formed. The curve rises rather suddenly in the first three-quarter hour, then falls in an irregular wave to the two and a fourth hour period, when it begins its secondary rise higher than the digestive rise and retains it to the end of collection. Secretion was obtained in these cases an average of only a little over two hours as compared to two and three-quarter hours in chronic appendix cases. Food was present in all of the specimens of secretion in only one case, in the others it was absent in the last fifteen minutes to three-quarter hour, while in the chronic appendix cases, though secretion was obtained three-quarters of an hour longer, food was present in three cases in all of the specimens. A two-year gastrojejunostomy is interesting from the high actual acidity with a secondary rise at the end, and the length of time secretion was obtained, three and a half hours. This rather increased length of time corresponds to other observations.

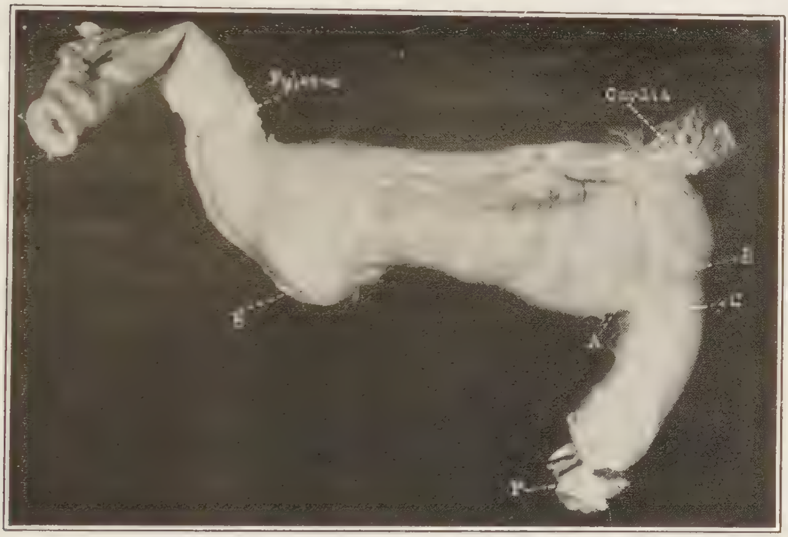

FIG. 14.—Pawlow pouch made in Experiment 5. Line *E-A* is the line of the incision through the stomach wall. From *A* to *B* the mucosa and submucosa have been cut and peeled back from the muscle after which the ends are invaginated along the line *A-B* and in the small stomach at right angles, *C* to *D*. The point *D* is located on the posterior wall opposite *C*. The pouch is completed by invaginating the stomach wall from *A* to *F*, leaving the small opening at *F*. The incision through the main stomach is completely closed from *A* to *E*.

The gastric symptoms in chronic appendicitis may be caused primarily by a reflex spasm of the pylorus with secondary changes in secretion and acidity (Aaron), or, according to Fenwick and McGuire, the gastric secretions may be changed primarily, with the other changes secondary to the irritation of a hyperacidity. Fenwick believes the constant excess of free HCl gives rise to a spasmodic closure of the pylorus and also excites a violent gastritis often with interstitial hemorrhages. He believes that 12 per cent of the cases of hypersecretion are due to disease of the appendix and that there is usually an increase both in quantity and acidity, when active irritation of the appendix is present. Paterson says that the appendix influences the gastric secretion but thinks it due to intestinal stasis rather than pyloric spasm. Ochsner says that there is undoubtedly a contraction of the ileocecal valve during an acute exacerbation of appendicitis. This in turn may give rise to a contraction of the duodenal and pyloric sphincter and in this way the normal passage of food from the stomach is impaired. Long and short, or local, reflex nerve paths to the stomach from the appendix and intestine have been demonstrated clinically and experimentally.

In my experimental observations I used the Pawlow pouch in order to obtain pure juice, and found it of value in controlling operative and postoperative hemorrhage to run a buttonhole suture around the incised stomach wall before invagination. In order to lessen the tendency to breaking down of the mucosa between the main stomach and the pouch I invaginated the cut mucosa and sub-mucosa as Keeton has suggested, not so that the closed edges of the two stomachs fell against each other, but so that they formed a cross

C
E..........A + B (Fig. 14).
D

In my experiments on dogs, lesions similar to chronic appendicitis with adhesions in the human were attempted. The cecum of the dog forms a rather long spirally twisted appendix. A stenosis of this cecum and adhesions to the colon, ileum and abdominal wall were produced.

ANIMAL EXPERIMENTS

1. Pawlow pouch, January 17, 1917. Lesions of cecum, January 24, 1917. Slightly inflamed cecum removed and adhesions freed, January 29, 1917. Posterior gastrojejunostomy, March 5, 1917. Dog chloroformed,. May 28, 1917. Gastro-enterostomy and Pawlow pouch results good.

2. Pawlow pouch, February 23, 1916. Collections. Lesions of cecum, April 10, 1916. Posterior gastrojejunostomy, May 8, 1916. Collections. Dog chloroformed, August 4, 1916. Necropsy: adhesions of cecum to colon, ileum and abdominal wall. Gastrojejunostomy opening patent.

3. Pawlow pouch, March 2, 1916. Lesions of cecum, March 27, 1916. Dog chloroformed, April 2, 1917. Wound infection. Definite inflammation of cecum.

4. Pawlow pouch, October 20, 1916. After collections, lesions of cecum, November 20, 1916. Collections. Reoperated. Dog chloroformed, November 25, 1916. Necropsy: acute inflammation of cecum and peritonitis.

5. Pawlow pouch, November 27, 1916. Collections. Lesion of cecum, December 13, 1916. Inflamed cecum removed, December 28, 1916, adhesions to ileum, colon and abdominal wall freed. Dog chloroformed, January 13, 1917.

6. Pawlow pouch, December 1, 1916. Collections made similarly to experiment 5 as a normal control.

7. Pawlow pouch, January 2, 1917. Lesions of cecum, January 12, 1917. Distemper. Dog chloroformed, January 20, 1917. Necropsy: adhesions and stenosis of cecum.

8. Pawlow pouch, January 5, 1917. Lesions of cecum, January 15, 1917. Cecum removed and adhesions freed, January 20, 1917. Dog chloroformed, February 28, 1917. Necropsy: small communication between the two stomachs. Ulcer at suture line.

9. Pawlow pouch, January 16, 1917. Lesions of cecum, January 24, 1917. Acutely inflamed cecum removed. Peritonitis. Dog chloroformed, January 30, 1917.

10. Pawlow pouch, January 19, 1917. Lesions of cecum, January 26, 1917. Collections. Cecum removed, January 29, 1917. Distemper. Dog chloroformed, February 13, 1917.

11. Pawlow pouch, November 24, 1916. Collections. Emaciation and vomiting. Dog chloroformed, December 13, 1916. Necropsy: marked hour-glass contraction of stomach. No other pathology.

The following are tabulations of animal experiments illustrative of my results, the column under "pH," shows the acidity determined by the gas-chain method. Under "HCl" is placed the dimethyl amino azobenzene and under "Total" the phenolphthalein, acidity, determined by the titration method.

Experiment 1.—One of four test meals from Pawlow pouch before lesions were produced. Test meal, 75 gm. Hamburg and 2 gm. peptone:

Hr.	pH	HCl	Total	C.c.
1	1.19	94	106	6½
2	1.27	72	94	1½
3	3.43	0	54	1
4	...	...	...	½

After production of stenosis of cecum and adhesions. One of five test meals:

Hr.	pH	HCl	Total	C.c.
1	1.18	100	110	2½
2	1.18	90	104	1½
3	1.30	62	82	1
4	....	...	...	½

After removing cecum and freeing adhesions. One of seven test meals, one to twenty-three days after operation:

Hr.	pH	HCl	Total	C.c.
1	1.22	98	119	3
2	1.23	96	110	2½
3	....	66	82	2
4	....	...	...	1

One typical test meal from five tests, four to seventeen days after a gastrojejunostomy:

Hr.	pH	HCl	Total	C.c.
1	1.08	84	98	5
2	1.06	102	114	6
3.4	1.01	106	118	8
5	1.03	98	110	4
6	1.01	100	112	2

Experiment 5.—Four test meals made from Pawlow pouch. Illustrative meal after 75 gm. Hamburg and 2 gm. peptone:

Hr.	pH	HCl	Total	C.c.
Continuous secretion	1.43	42	48	1
1	1.28	60	66	4
2	1.32	60	66	5
3	1.33	68	74	3½
4	1.60	80	86	3
5	1.52	54	60	3
6	1.50	64	68	2½
7	1.26	64	68	2
8	1.43	42	60	1½

After production of stenosis of cecum and adhesions. One of two test meals:

Hr.	pH	HCl	Total	C.c.
Continuous secretion	1.35	78	86	4
1	1.20	74	84	20
2	1.20	64	72	14
3	1.15	90	100	10
4	1.14	84	88	8
5	1.33	82	88	8
6	1.36	80	82	7
7	1.25	80	88	10
8	1.26	76	82	9
9	1.52	80	86	6

Twelve days after removal of inflamed cecum. No appetite. Test meal given by tube:

Hr.	pH	HCl	Total	C.c.
Continuous secretion	1.10	104	116	3
1	1.30	94	104	2½
2	1.30	98	106	3

Experiment 8.—Average of five test meals from Pawlow pouch. Test meal, 75 gm. Hamburg and 2 gm. peptone:

Hr.	pH	HCl	Total	C.c.
1	1.25	85	105	4½
2	1.18	92	109	6½
3	1.22	70	80	2
4	1.49	80	95	1½
5	1.65	50	78	2
6	1.18	95	103	1
7	1.20	92	100	1

After production of stenosis and adhesions of cecum. Average of four test meals:

Hr.	pH	HCl	Total	C.c.
1	1.23	74	85	7
2	1.16	86	96	5
3	1.16	62	87	4½
4	1.18	74	89	1½
5	....	28	54	½
6	....	24	48	½

After removal of long cecum. Average of five test meals:

Hr.	pH	HCl	Total	C.c.
1	1.17	116	128	8
2	1.15	121	133	10½
3	1.16	113	125	5½
4	1.16	90	106	3
5	1.20	108	118	1
6	1.20	108	118	1

Experiment 10.—Average of three test meals from Pawlow pouch. Test meal, 75 gm. Hamburg and 2 gm. peptone:

Hr.	pH	HCl	Total	C.c.
1	1.26	89	104	3
2	1.22	74	94	1½
3	....	...	...	½
4	1.4	72	96	½

After production of stenosis of cecum and adhesions. Average of three test meals:

Hr.	pH	HCl	Total	C.c.
1	1.14	102	116	4
2	1.13	107	122	1½
3	1.27	100	110	1
4	1.18	100	109	1
5	1.18	100	108	1

After removal of cecum and freeing of adhesions. Average of five test meals:

Hr.	pH	HCl	Total	C.c.
1	1.12	118	130	3
2	1.14	116	124	4
3	1.12	116	119	1½
4	1.14	110	114	1
5	1.14	110	112	½

RESULTS OF EXPERIMENTS

In considering the results of the animal experiments, there was found to be a definite increase in secretion in nearly one-half of the cases after lesions of the cecum were produced. In one case there was also an increase in continuous secretion; in the others there was a hypersecretion with a slightly longer period of flow. After removal of the "cecum" there was also a marked increase in quantity in one case and slight increase in another. The actual acidity after the lesions, as well as after the removal of the "cecum," was slightly higher than that ordinarily found corresponding to an increased flow of secretion. After gastrojejunostomy (Experiments 1 and 2) there was a decided increase in the rate of secretion in both cases as well as a prolonged flow of juice in one case. The acidity was slightly increased after gastrojejunostomy, associated with a more rapid rate of flow. After hour-glass contraction of the stomach in three cases there was no decrease of acidity, although frequently a decrease in such cases has been found clinically. There was a slightly increased rate of flow in some instances, in others a decreased rate, associated with emaciation and vomiting. One case (Experiment 11) is listed.

SUMMARY OF CLINICAL AND EXPERIMENTAL WORK

In a group of surgical cases, it has been shown that the curve of acidity may rise higher at the end of digestion than it has during the digestive rise. After certain surgical lesions have been made on the gastro-intestinal tract of animals, it is demonstrated that there is a slight increase in acidity in the secreted gastric juice; in some reflex manner, however, lesions of the cecum or other changes may cause an increased rate of flow. There must be some disturbance of the factors concerned in neutralization of the acidity associated with the factors controlling the discharge of chyme through the pylorus. The contour of the curve of acidity must be influenced by the food and fluids present, the intensity and duration of the appetite and food secretion, the emptying time of the stomach, the regurgitation of alkaline and duodenal contents, the gastric mucus and the saliva.

CONCLUSIONS

1. The clinical study of the gastric secretion must be done by examination of specimens taken at short intervals during digestion. Examination of a single specimen for comparative purposes is inexact and inadequate.

2. There is often a persisting high acid secretion after the digestive period. The digestive acidity may fall with a secondary late rise. Frequently surgical cases have this type of curve.

3. Clinically, the pH derived from the titration method is uniformly higher than the actual acidity as determined by the gas-chain method.

4. In animal experiments, after production of chronic inflammation of the long appendix of the cecum, with adhesions, after the removal of this appendix, after gastrojejunostomy and hourglass stomach, no definite increase in actual acidity of pure gastric juice was observed. There was an increased rate of flow and a prolonged flow in some cases.

5. The presence of increased acidity in the gastric contents in these surgical conditions must therefore be explained by factors noted in the summary and not to an actual increased acidity of the gastric juice.

DETERMINATIONS OF GASTRIC ACIDITY FOLLOWING GASTRO-ENTEROSTOMY*

PAUL A. WHITE

This problem was undertaken with a view to ascertaining the acidity of the gastric contents following gastro-enterostomy and other operative procedures for gastric and duodenal ulcers in a fairly large group of patients. The method of determining the gastric acidity is not new but has been studied in various series of patients by several authors. In reviewing previous investigations, however, I was unable to find that the postoperative acidity had been estimated in any series at a definite time after operation in all the cases. Gastric acidity estimations were made for patients tested postoperatively at various periods ranging from one to several months, and the results have been recorded as an average postoperative acidity for various procedures for the relief of gastric and duodenal ulcers. For example, Wilensky and Crohn report a series of thirty-seven cases of gastric and duodenal ulcers in which the preoperative acidity was determined. The postoperative results are averaged under headings such as, "one to four months after operation," "four to twelve months after operation," and "one to four years after operation." Smithies reports percentages of reduction in acidity for cases in which the determination was made, "soon after operation," "one to three years," and "three to five years," after operation. Also in the records which I have reviewed there has been no reference to any determinations made less than four weeks after operation. The periods range from four weeks to several months or years. In almost all the cases of the series presented herewith the determinations were made on the sixth and eighteenth days after operation.

It is a common observation of physicians accustomed to dealing with large numbers of gastro-enterostomized patients that the patients, as a rule, are enthusiastic over the almost immediate relief following operation. When after five or six days reaction is complete and the patients again receive food into the stomach, they are free from the distress which followed digestion only a few days before. Because of this striking relief it was thought desirable to record the gastric acidity as soon as possible after operation and, if feasible, make the determinations on the same postoperative day. If similar results were found previous work would be verified, and definite data would be furnished to associate relief from symptoms with a fall in acidity.

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In conjunction with the work in making estimations of acidity six days following operations on patients who were still in the hospital, estimations were made after the patients' discharge from the hospital. The latter range from thirteen to twenty-seven days after operation but nearly all on or near the eighteenth day. A number were made on patients whose acidities had been determined on the sixth day. In all the cases studied preoperative estimations of acidity had been made. From facts obtained the following comparisons were made:

1. Preoperative gastric acidity with that found the sixth day after operation in the same patients (118 patients).

2. Preoperative acidity with that found the eighteenth day in the same patients (169 patients).

3. Preoperative acidity with that found the sixth day and the eighteenth day in the same patients (forty-nine patients).

Table 1.—Average Preoperative Acidity and the Postoperative Acidity on the Sixth Day in 118 Patients

Patients	Preoperative acidity		Postoperative acidity		Acid reduction		Reduction percentage	
	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid
118	58	42	31	18	27	24	46	57

Table 2.—Average Preoperative Acidity and Postoperative Acidity on the Eighteenth Day in 169 Patients

Patients	Preoperative acidity		Postoperative acidity		Acid reduction		Reduction percentage	
	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid
169	59	43	37	23	22	20	37	45

Table 3.—Average Preoperative Acidity and Postoperative Acidity on the Sixth and Eighteenth Days in Forty-nine Patients

Patients	Preoperative acidity		Postoperative acidity sixth day		Acid reduction		Reduction percentage		Postoperative acidity eighteenth day		Acid reduction		Reduction percentage	
	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid
49	60	45	29	17	31	28	51	62	33	19	27	26	45	57

For comparison separate estimations were made in eleven duodenal ulcer patients in whom the ulcer was excised and no gastro-enterostomy done.

Preoperative and postoperative estimations of acidity within three weeks of the operation were made in a total of 238 patients. In all but eleven of these a posterior gastro-enterostomy had been done, regardless of the direct treatment of the ulcer itself. In all the gastroenterostomies the short, or "no-loop," anastomosis with the jejunum was performed, the opening in the jejunum being but 10 or 12.5 cm. from the ligament of Treitz, which marks the duodeno-jejunal juncture.

The stomas for the most part were made uniformly about 6.25 cm. in length and were all sutured with absorbable material. A few silk sutures may have been used at the ends of the opening, where the stress comes as the jejunum turns down from the anastomosis, but these were placed only in the serosa. No Murphy buttons were used.

In the eleven patients with duodenal ulcers in whom gastroenterostomy was not done, knife or cautery excision of the ulcer was carried out, and the line of incision was in the longitudinal axis of the gut, closure being made transversely after the Heineke-Mikulicz plan except that in most cases the incision probably did not extend through the pylorus. These cases are grouped separately, but the number is too small to permit of conclusions with regard to the effect of such treatment.

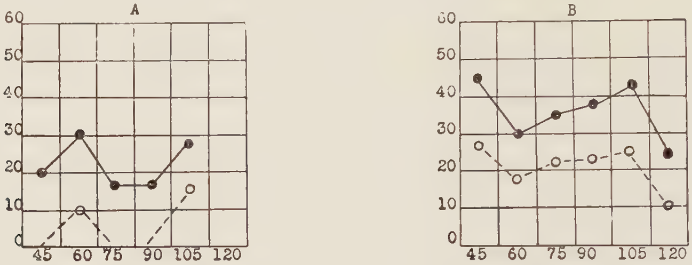
In thirty-eight of the 227 cases, ten of duodenal ulcer and twenty-eight of gastric ulcer, in addition to the gastro-enterostomy the ulcer was dealt with directly. The Balfour cautery was used in most of the cases of gastric ulcers; the others were excised by knife. Knife or cautery excision or ligation of the arteries supplying the ulcer area were the methods of dealing with the duodenal ulcers that were operated on directly.

In the group of 227 cases on which this study is based, a new outlet was made in the stomach. The opening was similarly located on the stomach wall and in the jejunum, and was of nearly uniform size in all the cases. The titrations were made on definite postoperative days, on the sixth or eighteenth days, or on both.

METHODS OF OBTAINING GASTRIC CONTENTS

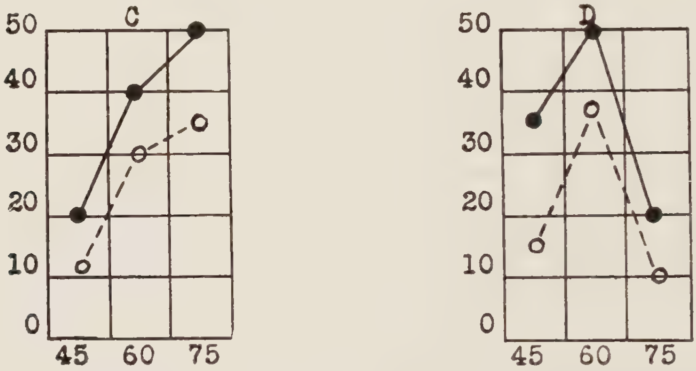
The specimens obtained on the sixth day were taken while the patients were still in the hospital. They had had their supper the night before, usually a cooked cereal, fruit, toast, and tea. If desired, milk was given in small quantities during the day and night until midnight. Before the patient had had breakfast, about 5:30 a.m. in these cases, the test-meal, 200 c.c. of beef boullion prepared by dissolving a boullion cube in hot water, was given. Only 200 c.c. were given to avoid any risk of gastric distension. Forty-five minutes later the first specimen was taken, followed by two others fifteen minutes apart. This carried the fractional acidity test over a period of one hour and a quarter after taking the meal. The routine test-meal in the gastric laboratory at the Mayo Clinic is 400 c.c. of fluid given with about 38 gm. of arrowroot crackers.

The specimens that were obtained on or near the eighteenth day were taken by routine methods at the gastric laboratory after the patient had been discharged from the hospital. Less than half of those from whom the specimens had been obtained at the hospital reported for a subsequent examination at the gastric laboratory. The patients tubed at the gastric laboratory had had their ordinary meal the night before followed by a few raisins; then the test-meal was given without the patient having taken breakfast. The first specimens were aspirated forty-five minutes later. In most cases subsequent aspirations were made at fifteen-minute intervals until four or five specimens had been obtained. This carried the fractional acidity determination over a period of one hour and three quarters. In noting the acidities and taking the averages the highest acidities found during the estimation were used throughout. Only three specimens, carrying the test over a period of one hour and fifteen minutes following the test-meal, were obtained from the sixth-day patients. This was not because of certainty that the highest digestive acidity would appear within this limit but because of a time limitation in which to do the work each morning, and because of a desire to relieve the patient of the tube as soon as possible.



Case A272297. Eighteen days after operation.

Case A270693. Fifteen days after operation.



Case A276268. Six days after operation.

Case A275718. Six days after operation.

Fig. 15.—Typical postoperative acidity curves.*

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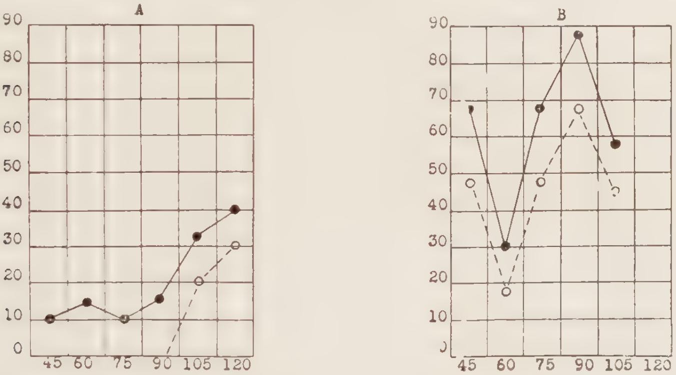
*The solid black represents total acid; the circles represent free acid. The abscissæ represent acidity; and the ordinates represent time in minutes after the test-meal.

The results in the series in the Mayo Clinic support the evidence obtained elsewhere that the highest acid values of the digestive period were obtained in the cases tested on the sixth day, even though the aspirations were carried only to one and one quarter hours following the test meal (Fig. 15 A, B, and D).

The curves of acidity values in some cases following gastro-enterostomy are very erratic. The total acidity may rise gradually from the beginning to the end of the test, about two hours. Free acid may not appear until the third or fourth aspiration, one and one half to one and three quarters hours (Fig. 16 A). Again, total and free acid may appear and increase rapidly to a maximum by the second aspiration, one hour, fall markedly by the third aspiration, one and one quarter hours, and sweep to a high level very soon (Fig. 16 B). In fact all variations of curves are found, but a close comparison shows confirmation of the rule stated by other observers.



Case A265915. Eighteen days after operation. Free acid did not appear for one and three-quarter hours after the test-meal.

Case A185042. Eighteen days after operation. The primary rise is high but the secondary rise exceeds it.

FIG. 16.—Atypical postoperative acidity curves.*

*The solid black represents total acid; the circles represent free acid. The abscissæ represent acidity; and the ordinates represent time in minutes after the test-meal.

RATIONALE OF GASTRO-ENTEROSTOMY

A review of the literature discloses the difficulty with which a definite experimental basis is established for the theories with regard to the cause and cure of chronic gastric and duodenal ulcers. One very definite conclusion may be drawn, however, that is, gastro-enterostomy is a drastic stroke in a vicious cycle. The evidence to support this is somewhat as follows: Something causes ulcer. Most recent writers incline toward the infective theory, which postulated selective localization from a chronic focus, as claimed by Rosenow. The ulcer causes hyperirritability and spasm which produces pain. Hypersecretion and hyperacidity follow; associated with these factors are retention, prolongation of the "digestive phase" of the gastric cycle, and the opportunity for long contact of gastric juice high in acid and pepsin with the ulcer area. These ingredients are important in sustaining the low grade inflammatory condition in the mucous

TABLE 4.—AVERAGE PREOPERATIVE ACIDITY AND POSTOPERATIVE ACIDITY IN PATIENTS WITH GASTRIC ULCER

Patients	Preoperative acidity		Postoperative acidity sixth day		Acid reduction		Reduction percentage		Postoperative acidity eighteenth day		Acid reduction		Reduction percentage	
	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid
9	39	24	27	13	12	11	30	45						
19	49	35	..	..	..	..	..	..	38	13	11	22	22	62
5	37	22	19	6	8	16	21	72	19	7	8	15	21	68
Duodenal Ulcers														
109	59	44	33	19	26	25	44	56						
150	60	45	..	..	..	..	..	..	38	24	22	21	36	46
44	62	48	31	18	31	30	60	62	34	21	28	27	45	56

membrane and connective tissue and they encourage chronicity of the ulcer. Sustained chronicity only means repetition of the cycle, each time on a little higher plane of viciousness.

Rehfuss, after years of investigation of gastric problems, states that "rupture" of this vicious cycle is demanded in the treatment of chronic gastric or duodenal ulcers. He proposes to accomplish this by medical measures, that is, starvation, selected diet, sedatives, and lavage.

Operation effected the "rupture" in my series of cases. They show that high acidity does not continue throughout the whole of the digestive period in the postoperative ulcer cases as it does in the preoperative cases. Thus the "interdigestive" phase of the gastric cycle is prolonged.

The stomach is normal in size or smaller following operation, showing that the hypersecretion and retention have been eliminated. By removing the retention and hyperacidity the long contact of acid and pepsin with the ulcer area is prevented and alkali fluids are substituted. This should relieve the irritation to the ulcer and consequent tendency to chronicity. When the irritation is markedly lessened spasm and pain are relieved and the patient will declare that he is cured. This sequence of events will account for the striking relief these patients experience so soon following operation. Whether or not the ulcer heals promptly it is quite probable that instead of the previous vicious cycle with its gradually ascending malevolence a benign cycle with permanent ameliorating influence is substituted.

Tables 1, 2, 3, and 4 present the results of this investigation. Tables 1, 2, and 3 include both gastric and duodenal ulcer patients, on all of whom gastro-enterostomies were performed. The gastric ulcers are separated from the duodenal for purposes of comparison (Table 4). The results in a small group in which duodenal ulcers were excised and no gastro-enterostomy was performed are shown in Table 5.

TABLE 5.—AVERAGE PREOPERATIVE AND POSTOPERATIVE RESULTS IN PATIENTS WITH DUODENAL ULCER EXCISED WITHOUT GASTRO-ENTEROSTOMY

Patients	Preoperative acidity		Postoperative acidity		Acid reduction		Reduction percentage	
	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid	Total acid	Free acid
11	71	58	63	51	8	7	11	12

DISCUSSION OF TABLES

The reduction of acidity averaged about 50 per cent for all the groups. The eighteenth-day averages are always somewhat less in reduction than the sixth-day specimens. Wilensky contends that sooner or later the acidity climbs back to the height it held before operation. Eusterman believes that the postoperative acidity is permanently reduced from 20 to 40 per cent in 80 per cent of patients. If the acidity returns to its original height, the former train of symptoms may return temporarily, to disappear within a year after operation.

The percentages almost universally show more of a reduction of free acid than of the total acidity. This is interesting since the uncombined acid, with pepsin, is believed to be the ingredient that is instrumental in irritating the ulcer area and sustaining its chronicity.

The findings in the gastric and duodenal ulcers are only what would be expected since the gastric ulcers have not the high preoperative acidities of duodenal ulcers.

The group of duodenal ulcer cases with excision is small; the findings are at least suggestive, however, and indicate desirability of studying a larger group of cases.

CANCER OF THE STOMACH*

IVAN W. McDOWELL

The writer reviewed material at the Mayo Clinic, comprising 445 gastric cancers, or all cases in which resection was performed (399) or obtained at necropsy (forty-six) from January 1, 1905 to January 1, 1914.

The data recorded were based on:

1. The primary pathologic diagnoses made from the examination, in almost all instances, of the specimen immediately after its removal by Wilson or MacCarty.
2. A review of all photographs and sections made at the time of the original diagnosis.
3. A review of all sections of fixed tissues previously prepared from these cases.
4. From many cases the study of serial paraffin sections recently prepared and selected included, whenever possible, a section through the border and base of the ulcerating lesion.
5. A study of the clinical data with reference to the previous symptoms and subsequent history.

Of the 399 cases of gastric cancer from which the tissue containing the primary lesions was resected in the Mayo Clinic, 4.8 per cent showed ulcers with doubtful cancer in the border, 15.8 per cent showed ulcer with positive early cancer in the borders only of the lesion, 36.8 per cent showed ulcer with advanced cancer, and 42.6 per cent showed cancer in which the evidence of previous ulcer formation was doubtful.

Of the 46 cases of gastric cancer from which the tissue containing the primary lesion was obtained at necropsy, one case (2.2 per cent) shows an ulcer with doubtful cancer, seven cases (15 per cent) show ulcer with advanced cancer, and in thirty-eight cases (82 per cent) the evidence of ulcer previous to cancer formation was doubtful.

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* Abstract of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery, 1919.

The portion of the thesis not abstracted comprises a review of the literature, and a discussion and summary of the known facts with regard to etiology (heredity, infection, and chronic irritation), pathology, histopathology, diagnosis, treatment, and operative technic, and a bibliography.

The clinical and pathologic data of the development of gastric cancer on gastric ulcer are in close agreement with regard to (1) the average age of the patient at operation, (2) the average period of previous history suggestive of ulcer, and (3) the average number of months of acute symptoms. Such agreement of data from independent studies of this series of cases is not accidental.

It seems probable from a careful study of the clinical and pathologic evidence of this series of cases that gastric cancer rarely develops except at the site of a previous ulcerative lesion of mucosa.

ULCERS OF THE GASTRO-INTESTINAL TRACT WITH SPECIAL REFERENCE TO GASTRO-JEJUNAL ULCERS*

JOHN L. BUTSCH

The wealth of material in the Mayo Clinic suggested the desirability of a study of the clinical findings with regard to gastrojejunal ulcer, and also a study of the experimental acid phase of the condition, not so much the gastric acidity as the relation of the blood reaction to gastric digestion, ferment injection, duodenectomy, and so forth. My investigation led me to believe that the stomach conserves alkali for the body and that there is a reciprocal relation between the physiology of the blood proximal and distal to the division of the stomach and duodenum.

THE ETIOLOGY OF GASTROJEJUNAL ULCER

Ever since it became known that gastrojejunal ulcers follow gastroenterostomy, attempts have been made to discover the etiology of the condition. Why does the ulcer occur in such a low percentage of cases? Why is it not found more frequently since the same changes and the same mechanical, anatomic and physiologic changes have occurred? The difference in the time of the appearance of the ulcer, its position, and so forth, lead to the belief that the etiologic factors differ in different cases.

Many observers believe that infection is the cause of the ulcer. Mayo Robson believes that through lack of care of the mouth slight septic gastritis with hypochlorhydria is produced, which may lead to ulceration. He believes that all peptic ulcers are due to this infection, whether gastric, duodenal, or jejunal. Newman believes that these ulcers are of mycotic origin, there being first a mycotic necrosis of the mucosa, and then a peptic digestion.

The infection theory in the production of gastrojejunal ulcers has many adherents because in anastomosing the stomach and intestinal

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mucosæ, wounds are produced which become infected secondarily; these acted on by the hyperacidity of the gastric juice, become chronic. Schostak, Paterson, and Gould have studied the healing of gastro-enterostomy wounds and believe that ulcer is a direct result of the operation. Most gastro-enterostomies heal by secondary intention; they become infected and are changed to chronic ulcers by hyperacidity. The extent of the necrosis may be explained as due to mechanical measures, such as traumatism by instruments, the Murphy button, and even by suturing. Circulatory disturbances are given as a second cause. The circulation may be interferred with in several ways. The loop of intestine may be too short and cause tension, or, if the mesentery is kinked the blood supply may be impeded; the suture, too, may obstruct vessels; the segment of gut anastomosed to the stomach may be abnormally fixed; there may be pressure from the colon or stomach, arteriosclerosis of the vessels, which makes kinking more effective, or injury to the mucous membrane at the time of the operation, or later by food. The peptic factor is the third hypothesis advanced. Paterson, Kocher, Körte, and others hold to the hypothesis that the high acidity of the chyme kills the cells of the normally alkaline intestinal mucosa, which is subsequently digested by the pepsin. The free hydrochloric acid, not the total acidity, is the factor which causes the death of the cells. It is toxic to the mucous membrane which if its vitality is destroyed, can readily be digested by the pepsin.

Acidity or lack of alkalinity seems to play an important part in the formation of ulcers in or around the stoma. Ulcers in the afferent limb are rarely seen; either they appear just opposite the stoma or in the efferent limb, where the acid chyme acts. Thus in the "Y" operation we have a higher percentage of ulcers than in the gastro-enterostomies, or the gastroduodenostomies. Again, even in ulcers of the duodenum, the ulcer is high, and seldom more than 2 or 3 inches from the pylorus. It never occurs low in the duodenum. Bolton writes, "It appears, then, that any strength of hydrochloric acid above the normal can act as a protoplasmic poison for the gastric cells, and will add its quota to any other devitalizing influence and assist in bringing about self-digestion."

If acid is the toxic agent that causes death of the cells, naturally alkali is its antidote. The cells of the mucosa must have alkali to neutralize the acid that is found with them. This increase of alkali in the blood of the stomach has been demonstrated, and will be discussed later herein. The duodenum, however, has not the power to increase or decrease the alkali content of its cells, so we have a much greater incidence of ulcer in the duodenum than in the stomach. For the same reason the point opposite the stoma and distalward is the site of election for ulceration following gastro-enterostomy.

Furthermore, since antipepsin and antiferments have never been demonstrated, it may be that this action which we have been calling anti, is merely one of alkalinity. It is a well known fact that few cells live in acid mediums; in order that cells may functionate and reproduce alkali mediums are necessary. The same is true of the gastric cells, of the duodenum or of the jejunum. Increased acidity kills, and death produces localized acidity in the tissues, which gives the pepsin a chance to be activated and digestion to progress. If the mucosa destroyed forms a gap too great for healing, a chronic ulcer results.

THE FREQUENCY OF DUODENAL AND GASTRIC ULCERS

The frequency of duodenal and gastric ulcers seems to be decided in favor of the former. In the Mayo Clinic many more duodenal than gastric ulcers are seen. Grüber's and Kreuzfuchs' necropsy records show quite the contrary. Moynihan finds many more duodenal than gastric ulcers.

THE POSITION OF THE ULCERS

The positions of the ulcers vary. On the gastric side the greater number are on the lesser curvature near the pylorus; most ulcers are near the pylorus (juxta pyloric region of Ewald). A number are on the posterior wall, and fewer are near the cardia and along the greater curvature. On the duodenal side they are mostly on the anterior surface within 2 inches of the pyloric ring. The pyloric veins make a good dividing line between gastric and duodenal ulcers. W. J. Mayo first called attention to the pyloric vein as a landmark in dividing gastric from duodenal ulcers.

EXPERIMENTAL RESEARCH

Extensive experimental research has been carried out with regard to chronic gastric ulcer. Greggio made a careful review of the literature, and I have quoted him liberally in order to give an idea of the numerous and various experiments. A true chronic ulcer is rarely produced experimentally. Acute ulcers which heal rapidly may be produced in various ways; Mann, whose experiments on ulcers following adrenalectomy are well known, has been able to produce them by many methods. Likewise Rosenow's work on the infectious theory of ulcer production is familiar to all.

Various chemical, physical, mechanical, physiologic, and biologic methods have been carried out on animals, such as rabbits, guinea pigs, and dogs to produce an ulcer. Virchow and Ebstein used phosphorus. Filehne and Bohn gave subcutaneous injections of arsenous acid. Jousset and Lefas injected tartar emetic. Majer and Coen tried progressive poisoning with acetate of lead. Overback tried the cutaneous use of mercurial inunctions. Saikowski gave subcutaneous injections of corrosive sublimate. Pilliet injected glycocolate of mercury. Peron injected alcohol. Silbermann injected pyrogallic acid and tried burning the skin. Aufrecht used cantharidin. Roy and Poncet used ergotine and scillitoxin. Westphal used pilocarpin and physostigmin. Stich injected ptomaines. Rehfuss used the venom of certain lizards. Latzel injected the digestive juices of the stomach and intestines of one animal into another animal. Loepez injected the extract of the gastric mucosa, or the gastric juice of a hog. Bolton used cytotoxin or gastrotoxic serum. Gundermann used an extract of liver. Favre used the blood of a uremic person. Vassale and Sacchi extracted burned tissue. Lang and Castel glazed the skin. Special organs have been taken out. Gibelli, Latzel, and Mann have taken out the adrenals. Müller and Küllicher removed the liver. Boccandi and Falcone removed the thyroid.

The vascular supply has been modified by the injection of wax emboli. Panum, Prevost and Cottard injected tobacco into the aorta. Payr injected dermatol and India ink into the gastro-epiploic arteries and veins. Chessin and Feldmann injected lycopodium. Kobayaski injected liquid paraffin infected with staphylococci in order to produce ischemia by mycotic emboli.

Wilkie tried to produce retrograde embolic processes. Frederich and Hoffman ligated the umbilical veins with aseptic precaution. Otte and Gandy ligated the epiploic veins and the mesenteric veins. Sapiejko burned the omentum, von Eiselberg ligated it, Friedrich resected it.

Baron ligated the vessels of the stomach. Pavy and Matthes did the same, but in addition injured the mucosa mechanically, or chemically with hydrochloric acid. Fenwick and Gunidermann ligated the portal vein to produce stasis.

Changes in the constituency of the blood have been made by producing acute anemia with perchlorid of iron, pyrogallic acid, pyrodin and a combination of pyrodin anemia and the injection of dermatol into the gastric veins (Chessin and Feldmann). Silbermann and Fütterer produced a pyrogallic anemia, and at the same time ligated the arteries to the stomach. Gibelli tried bleeding, and at the same time traumatic lesions of the gastric walls. Zironi injected pyrodin, and at the same time resected the pneumogastric nerve. Anemias have been produced to retard healing in other experimental methods. Frouin produced a stasis, gave saline alimentation, and then hydrochloric acid. Lutzol fixed the duodenum and thus prevented the normal drainage of gastric juices. Loepez injected gastric juice and extracts of gastric mucosa.

Artifical hyperchlorhydria has been associated with other lesions, according to Matthes, with direct lesions of the mucosa, according to Koch and Ewald, with lesions of the medulla, according to Saitta, with resection of the pneumogastric nerve and ligation of the gastric vessels. Borszeky made ulcers at the gastro-enterostomy opening by producing a pyloric stasis and instillating hydrochloric acid. Stuber made gastric ulcers by producing pyloric insufficiency in such a manner that the pancreatic juice flowed back into the stomach. At the same time the dogs were fed in order to produce as little acidity of the stomach as possible.

The effect of trauma has been studied by Matthes and Gibelli. They produced direct lesions of the gastric mucosa. These wounds healed rapidly. Foreign bodies and caustics have been injected to produce trauma. Parry and Samuelson used concentrated hydrochloric acid. Sternberg used heat. Sternberg and Decker used hot foods. Matthes sutured the mucosa in rings to the muscular coats and noticed hard ulcerations. Fiori produced pyrodin anemia, then made a direct lesion, and thus produced a lasting loss of substance. Clairmont reports direct lesion of the mucosa associated with vessel ligation so that the two correspond. Fiebich did the same thing, but the results do not correspond. Local infection and hyperchlorhydria have been tried. Burning of the stomach with small tubes of hot porcelain and at the same time injecting phosphoric acid intravenously to kill the antipepsin was tried by Katzenstein.

Infection too, has had its advocates. Cohn injected pus into the arteries. Lebert injected it into the peritoneal cavity. Bauer injected the *Bacillus coli.* Wurtz and Leudet injected the *Bacillus lactis;* and Charrin, the *Bacillus pyocyaneus.* Favre injected an organism extracted from the blood of a patient with eclampsia. The monumental work of Rosenow in the field of infection is well known. Turk and Bauer kept animals undernourished with food infected with *Bacillus coli.* Singer mixed the food of animals with excreta. Filtered cultures of the *Bacillus pyocyaneus* have been injected by Charrin. Enriquez and Hallion injected diphtheria toxin. Claude injected tetanus toxin. Bolton injected gastric toxin. Wilkie produced thrombosis and septic emboli of the omentum. Kobayaski tied the cecum of a dog so that the peritoneum would become inflamed and thus cause ulcer.

Certain experiments show a relation of the lesions of the central and peripheral nervous systems and the formation of ulcers of the stomach and duodenum, for example, lesions of the thalamus; cerebral peduncles; the protuberances; the bulb; after burning of the cerebral surfaces (Brown-Séquard); lesions of the tubercles quadrigeminii or the hemispheres (Ebstein); and section of the cervical cord; bilateral lesions of the anterior and posterior roots of the fifth to eighth dorsal segments (Schupfer); excitation of the pneumogastric in the neck (Thalma); lesions produced by exciting the nerve subdiaphragmatically (Lichtenbelt); lesions formed by causing neuritis of the pneumogastric nerve in the neck, or in the abdomen by burning the nerve, or by the injection of alcohol. Donti's and Korte's results from section of the vagus in the neck were negative; only Saitta obtained any positive results when he also gave the rabbit hydrochloric acid. Section of the vagus in the thorax has given variable results; Krehl and Fritsch obtained negative results; Kawamura at times obtained positive results; abdominal section of the nerve gives the same results; Ophüls and Kobayaski have produced ulcers; Grünsburg and Lunch have failed to produce them; Marchetti by double ligation of the abdominal vagi has produced chronic ulcers; Lewin produced hyperemias, gastro-intestinal hemorrhages and mucous ulcerations by extirpating the celiac plexus; Budge and Lustig failed with the same operation. Kawamura succeeded, Kobayaski failed to produce the lesion or irritation respectively of the celiac plexus. Brancati ablated the paravertebral lumbar sympathetics and produced lesions; Vedova did the same by injuring the great splanchnic, Duranti by injuring the small splanchnic; Lilla's simultaneous lesions of the celiac plexus and pneumogastric produced small punctate hemorrhages; Samuelson had negative results even with the addition of injection of hydrochloric acid; Auror took away all the nerve supply of the stomach; the movements were diminished; the reflexes were suppressed; and ulceration occurred.

The gastric wall has been injected with adrenalin (Rosenbach and Eschker), with formalin (Borszeky), with gastrotoxic serum (Bolton). Tokuo Suzuki obtained lesions with the same agents injected into the gastric vessels, but they healed rapidly. Licini by the use of apomorphin has been able to convert some of these acute lesions into chronic lesions.

The foregoing experiments are not, however, to be considered positive, when compared with the *ulcus rotundum* of Cruveilhier. Different investigators, using the same experiment, vary in their results. Many methods produce lesions varying from small hemorrhages to destruction of the wall of the stomach and acute ulcer formation; such ulcers heal. The lesions following injury to the central nervous system are necrotic and occur also in other organs.

No one cause can be assigned for the formation of ulcer. Each case has its own special cause and whatever this may be, the preferable treatment is gastrojejunostomy. In the larger number of cases this operation effects cure, in some cases only improvement, and in a few cases the same symptoms remain with changed or added attributes. Attention is especially directed to the latter group since they include the greater percentage of gastrojejunal or jejunal ulcers. Just why these ulcers occur still remains a problem in surgery. Gastro-enterostomy seldom heals primarily; some parts of it may, but the greater portion of it heals by secondary intention.

THE HEALING OF THE GASTRO-ENTEROSTOMY STOMA

Harvey and Flint have given detailed reports of the healing of the gastro-enterostomy stoma. Changes occur about 7 mm. from the gastro-enterostomy line. The chief cells which are normally the cells that make ferments are changed to mucus-forming cells. The process begins at the line of contact of the two mucous membranes and in about three weeks extends to 7 mm. around the stoma. In the next 3 mm. radially around the stoma the ferment cells have a tendency to this change, but do not undergo a complete transformation. After one month a reverse transformation begins and the same cells become ferment cells. It takes fully six and one-half months to complete this process. After this the glands, up to the suture line, do not differ from those remote from it.

When the gastro-enterostomy has produced only a slight disturbance of the circulation there is a minimum of inflammatory reaction, and healing occurs by first intention. The infolded serous surfaces promptly adhere by throwing out a fibrinoplastic exudate, and this also extends along the entire line of the incision. After twenty-four hours the mucosa has regenerated and after from forty-eight to seventy-two hours any defect in mucosa may be covered. All that is necessary to complete the healing is the organization of the exudate. Such a process many be completed in from five to fourteen days.

When the circulation to the mucous membrane of the stomach and intestine has been much disturbed, the process is much slower and there are degenerative processes preceding the reparative. The mucous membrane, for varying spaces around the gastro-enterostomy, is destroyed and must be replaced. The destructive processes last about seven days, depending on the extent of the injury. After this time the restorative process begins and is completed at about the fourteenth day. The regeneration of the muscularis mucosa and the tunica muscularis takes somewhat longer.

The regeneration of the intestinal mucosa takes place from the crypts. In the area of the trauma the crypts return to their embryonic form. The epithelium flattens as it passes up from the crypts to the exudate, where it penetrates its substance and forms a single layer of squamous cells. From this layer young crypts extend down into the organizing exudate and there produce new growing centers. After the restoration of the epithelium is complete the differentiation into typical goblet cells and regular columnar cells takes place.

The regeneration of the gastric mucosa generally begins from the less differentiated epithelium around the mouths of the gastric glands or from the tubules that have returned to their embryonic form. As in the intestine the new-formed epithelium flattens as it passes up on the exudate which it often penetrates. From this sheet of epithelium new tubules are produced by invaginating into the substance of the exudate. The glands are at first embryonic but later assume their normal character. The muscularis mucosa begins to regenerate about the second week. It may be a complete regeneration of the muscle, or the ends may be connected with connective tissue strands. The tunica muscularis may do about the same thing. It may heal completely or it may be connected by new-formed connective tissue. The intestinal epithelium is not modified by the gastro-enterostomy. It heals well in the presence of the gastric juice, due to antiferments, or to the neutralization of the juice with *succous entericus.*

It should always be remembered that the new formed anastomosis is the site of a healing ulcerated surface for a period of fourteen days, that this healing is not always complete; and that the number of gastrojejunal ulcers is increasing, that is, their diagnosis is more and more sure.

The suture has been held responsible for the failure of the gastro-enterostomy to heal. Silk or linen sutures have often been found at the site of an old ulcer. This seemed a probable explanation of the finding until the abandonment of the silk and linen for the catgut suture. However, it is safe to say that the sutures were a factor but not the only one in retarding the reparative process.

OBSERVATIONS ON GASTROJEJUNAL ULCER

It was not until eighteen years after Wölfler's first gastro-enterostomy that a gastrojejunal ulcer was observed. The observation was made by Braun, in 1899, in a patient who had had a posterior gastrojejunostomy eleven months before for pyloric obstruction. The operation had not given him complete relief, the vomiting continued and his condition became so distressing that he sought hospital relief. His stomach was dilated below the umbilicus. With treatment he improved for a short time. On the second day after his third admission to the hospital he died. Necropsy showed a perforated jejunal ulcer in the afferent limb about 1 inch below the anastomosis. Peritonitis was general. The stoma was quite large.

After the report of this case many other observations were made. The first statistical report of twelve cases from the literature, was made by Kieffer in 1902-1903. In 1904 Tiegel reported six cases and collected sixteen others from German literature. In 1907 von Roejen reported seventy-eight cases, to which were added fourteen others by Petren in 1911. Further work was done by von Schostak, Polya, and others. Lieblein, in 1915, reported 129 cases. In France the first case was reported by Quenu in 1902. In England the first case was reported by Mayo Robson in 1904. In the same year Hamann reported the first case in America. Then followed the work on this interesting problem by Moynihan, the Mayos, Balfour, Carman and others.

In 1915 Balfour and Carman reported thirteen cases of gastrojejunal ulcers from the Mayo Clinic. Up to this time (April, 1919) there have been sixty-nine patients operated on. Forty-four followed operations performed in the Clinic, and twenty-five performed elsewhere. The present report concerns a group of forty-four cases.

STATISTICS

From January 1, 1906, to April 1, 1919, 3,480 patients with ulcer, 3,175 duodenal, and 305 gastric, were operated on in the Mayo Clinic. In the duodenal ulcer cases posterior gastro-enterostomy was performed in 3,161 (99.5 per cent). In fourteen (0.44 per cent) anterior gastro-enterostomies were performed. In 154 cases (4.8 per cent) in addition to a posterior gastro-enterostomy the pylorus was blocked. In 847 cases (26.6 per cent) perforation was found at the time of the gastro-enterostomy. In 977 cases (30.7 per cent) obstruction was found. In the gastric ulcers 279 (91.47 per cent) posterior gastro-enterostomies and twenty-six anterior (8.5 per cent) were performed. The pylorus was blocked in twenty-one cases (6.8 per cent). Perforation was found in 142 cases (46.5 per cent), and obstruction in seventy-three cases (23.9 per cent). The gastric ulcers showed a greater tendency to perforate, 46.5 per cent as compared to 26.6 per cent duodenal. The duodenal ulcers had a greater tendency to obstruct, 30.7 per cent as compared with 23.9 per cent gastric ulcer.

Eighteen of the forty-four patients on whom posterior gastro-enterostomy was performed had a high acidity before operation. In only six patients was it higher after operation. Four patients, however, had a higher acidity after the posterior gastro-enterostomy than before.

There were 2,689 males (77.3 per cent), and 791 (22.7 per cent) females in the series. In the duodenal cases (3,175), 2,453 (77.2 per cent) were males, and 722 (22.4 per cent) were females. In the gastric cases (305), 236 (77.3 per cent) were males, and sixty-nine (22.6 per cent) were females. In the gastrojejunal cases (sixty-nine), sixty-three (91.3 per cent) were males, and six (8.6 per cent) were females. The incidence of gastrojejunal ulcers is comparatively much higher in the male.

Table 1.—Miscellaneous

	Cases
Gastrojejunal ulcers following operation for gastric ulcer	6
Gastric ulcers no bleeding before first operation	4
Gastric ulcers melena before and after first operation	1
No blood before first operation but hematemesis and melena afterward	1
Gastric ulcers with perforation at first operation	3
Gastrojejunal ulcers with perforation at first operation	4
Gastric ulcers with obstruction at first operation	1
Gastrojejunal ulcers with obstructions at first operation	3
Gastrojejunal ulcers following anterior gastro-enterostomy	2
Hematemesis before operation	1
Perforation at operation	1
Gastrojejunal ulcers with perforations and obstructions at operation	1
Gastrojejunal ulcers following posterior gastro-enterostomy which had thread or suture material in ulcer area	11
Gastrojejunal ulcers with thread or suture material in ulcer area	11
Average time between first operation and appearance of symptoms of gastrojejunal ulcer	23.3 months
Average time after onset of first symptoms of gastrojejunal ulcer before operation	22.5 months
Gastrojejunal ulcers following excision and posterior gastro-enterostomy for gastric ulcer	2
Gastrojejunal ulcer following cautery excision and posterior gastro-enterostomy for gastric ulcer	1
Gastrojejunal ulcer following partial gastrectomy and later posterior gastro-enterostomy for gastric ulcer	1

Table 2. Conditions Before Posterior Gastro-enterostomy

	Cases
Emesis with retention (3 with food remnants at test meal)	10
Emesis with bleeding (5 with blood at test meal)	16
Emesis with bleeding and retention (3 with blood at test meal; 1 with food remnants at test meal)	4
Emesis without other findings	16
Emesis and dilated stomach	5
Bile in gastric contents	2
Emesis with retention, dilated stomach and pyloric stenosis	1

Conditions After Posterior Gastro-enterostomy

Emesis with retention (1 with food remnants at test meal)	6
Emesis with bleeding (2 with blood at test meal)	7
Emesis with bleeding and retention (2 with food remnants at test meal; 1 with blood at test meal)	3
Emesis without other findings	18
Emesis with dilated stomach	2
Blood in test meal	1
Bile in gastric contents	2

Table 3.—Ages by Decades

Gastric ulcer

	Patients	Per cent
11–20 years	6	(1.9)
21–30 years	33	(10.8)
31–40 years	51	(16.6)
41–50 years	98	(32.1)
51–60 years	77	(25.2)
61–70 years	36	(11.8)
71–80 years	4	(1.3)

Duodenal ulcer

	Patients	Per cent
11–20 years	33	(0.7)
21–30 years	468	(14.7)
31–40 years	919	(28.9)
41–50 years	922	(29.0)
51–60 years	627	(19.7)
61–70 years	201	(6.3)
71–80 years	14	(0.4)
81–90 years	1	(0.03)

Gastrojejunal ulcers

Average age	41.8 years
Oldest male	69.0 years
Oldest female	54.0 years
Youngest male	22.0 years
Youngest female	25.0 years

PATHOLOGIC ANATOMY

Just as in their clinical relation, so also in their pathologic-anatomic relation, ulcers of the gastrojejunal type resemble those of the gastric and duodenal types. They have a great tendency to perforate and to form inflammatory tumors. According to Key, they also have a great tendency to hemorrhage. The resemblance between these ulcers has been noted by many observers. In form they are sharp-edged and funnel shaped, more substance of the mucous membrane being lost at the surface of the wall of the stomach than deeper. The perforations vary in size from mere needle-sized holes to the size of a twenty-five cent piece or even larger.

In some jejunocolic fistulas all traces of an ulcerative process seem to have disappeared. Paterson even with microscopic search was unable to locate any ulcerative process, but found wrinkled mucosa with inflammatory reaction. As the ulcer grows older, induration increases, the ulcerative process may increase and the inflammation around its neighboring organs, the mesentery of the small bowel, the retroperitoneal tissues, the anterior abdominal wall, the transverse colon, and so forth, may be involved. When the process does extend, inflammatory tumors are found which resemble very closely those formed in the stomach. These ulcers often penetrate into the anterior abdominal wall, into the rectus muscle, more often the left. In some cases covered perforations are found. The colon occasionally prevents the ulcer from perforating, at other times the colon in its protective rôle has not been able to accomplish its work and a fistula between it and the jejunum has formed. In these fistulas the mucous membrane is sometimes directly continuous and completely healed, all ulceration having been checked. These conditions often narrow the stoma and decrease its efficiency, so much so that symptoms of obstruction appear.

Usually there is but one ulcer, but there may be more. Key, Lion, Paterson, and Petren each found four.

The position of the ulcers is usually in or around the stoma. Many of them are on the jejunum just opposite the stoma, where the chyme would directly guard the intestinal wall. The efferent limb of the jejunum has more ulcers than the afferent. Roejen hesitates to associate an ulcer far removed from the stoma with the previous posterior gastro-enterostomy but prefers to think that it is a spontaneous jejunal ulcer.

SYMPTOMATOLOGY

Cases of gastrojejunal and jejunal ulcers are usually divided into two main groups. In the second group two subdivisions have been made:

Group 1. Perforation occurs into the general peritoneal cavity. None of the cases in the present series fall into Group 1; all were of a chronic type. There were, however, many in which the perforation had healed and had formed a tumefaction of more or less extent.

Group 2. Owing to the formation of local adhesions, perforation does not occur into the general peritoneal cavity. (1) The base of the ulcer points outward toward the abdominal parietes, and if perforation occurs adhesions to the abdominal wall may form a sinus. (2) Perforation may occur into a hollow viscus, or adhesions may form at the site of the ulcer. The mesocolon quite frequently prevents perforation into the peritoneal cavity.

In twenty-three of the sixty-nine cases perforation had occurred, six perforating toward the abdominal parietes and seventeen inward, either toward the colon or toward the transverse mesocolon. There were four colonic fistulas. In eighteen of the cases remnants of a former silk or linen suture were found. In one case a silkworm gut was found. The position of the ulcers in a high percentage of cases was in or around the stoma. A few of the ulcers were on the wall of the jejunum opposite the stoma and fewer still on the efferent limb. In one case in which operation was performed elsewhere, an ileal ulcer was found; the anastomosis had been made high in the ileum. In a few cases the ulcers were multiple.

The symptoms of gastrojejunal ulcers are much the same as those of other peptic ulcers. If a patient who has been in good health following a gastrojejunostomy, begins to complain of his former symptoms, which may have added or changed attributes, an ulcer on the stoma, or around it should be suspected. A complaint of hyperacidity or hypersecretion is still further evidence. The pain usually is constant, and if in addition a tumefaction can be felt, or if the abdominal wall is indurated, the diagnosis becomes reasonably certain. The x-ray now gives valuable aid in diagnosing such ulcers by showing deformity of the stoma.

TREATMENT

Since there are cases of gastrojejunal ulcer on record that seemingly have been cured medically and other cases that have healed spontaneously, it is reasonable to give the patient a chance of medical cure before surgical intervention is attempted. The treatment should be rest in bed, carefully directed diet, with an appropriate amount of alkali.

The acute perforations are surgical. After operation they fall into Paterson's Group 2. In these cases in which there are more or less protective adhesions the indications for surgical treatment are not always clear. However, many may be cured; 40 per cent of the patients treated for such perforations at the Mayo Clinic were cured, and nearly all were benefited.

The operative procedure to be carried out depends on the individual case. The point to be kept in mind is not to do too much. Patients who have extensive operations do not recover so well. The findings at operation indicate whether a plastic operation on the stoma, a cut off gastro-enterostomy, a Heineke-Mikulicz, a Finney pyloroplasty, a gastrogastrostomy, or a gastroduodenostomy, should be performed. In a few of our cases it was necessary to operate a third time before relief was obtained.

PROGNOSIS

Questionnaires as follows were sent to each of the sixty-nine patients:

We are interested to know what has been the state of your general health since your last operation here for stomach trouble, and we shall greatly appreciate a reply to the following questions:

1. Have you any stomach trouble now?
2. Is the trouble the same as it was before the first operation?
3. If it is different, tell in detail how it differs.
4. Do you have pain?
    - (*a*) If so, how often, and is it daily?
    - (*b*) What time of day?
    - (*c*) Does food ease it?
    - (*d*) Does soda ease it?
    - (*e*) In what part of the abdomen do you feel the pain?
5. Does food agree with you?
6. Did the last operation help you?
7. Give any other information you can about your present condition.

Reports were received concerning thirty-four patients. Two had died. The findings in thirty-two cases were summarized as follows:

In response to the question, "Have you any stomach trouble now?" there were thirteen frankly negative answers and ten frankly positive answers. Nine patients who had received much benefit made modified statements. The answers were: "Yes, some" (Case 86663), "Occasionally" (Case 51115), "Yes, a little" (Case 119616), "Very occasionally" (Case 145305), "Occasionally, but slight" (Case 102407), 'A little" (Case 118450).

Fifty-nine per cent of the patients who had secondary trouble after gastro-enterostomy were benefited, 40 per cent were absolutely cured, 31 per cent, according to their own statements, were not benefited, and need further consideration.

In response to the question, "Is your trouble the same as it was before the first operation," the replies in the frankly positive group to the first question were all positive with one exception. One patient still had pain although the location had changed. The pain before the operation was circumumbilical but, "since the operation it has shifted to the right side just inside the short ribs." The pain instead of being dull and growing, was sharp, and came on in attacks.

In the intermediate group the responses were again variable, "What little trouble I have now is like my former trouble" (Case 102407), "My pain is gone but I have gas which bothers me" (Case 119416), and, "I am better than I ever was, my occasional trouble resembles my original" (Case 86663). One patient (Case 118450) replied that she felt, "easier." Another patient (Case 122474) admitted that her operation had benefited her, but stated that her trouble, although recurring less frequently, was the same as before operation. Four of these patients admit frankly that the old trouble is gone but give other slight symptoms of distress. It is clear that the patients in this group were greatly benefited. In the frankly negative group in response to the first question, none of the patients had any of their former symptoms, they were without pain and were feeling well.

Most of the answers to the questions, whether or not there were any changes of symptoms from the original after the gastro-enterostomy, that is, whether the new ulcers at the stoma developed symptoms with their own attributes, were, that the trouble following the posterior gastro-enterostomy was the same as before the operation. Eight of the ten patients who were not benefited by the operation reported that their symptoms were the same, two wrote that their pain was different, located on the left side above the umbilicus, and that it was more constant.

In the intermediate cases, that is, cases in which only slight trouble remained after the last operation, the symptoms varied. The chief complaints were gas and acidity with some pain. The pain symptom in these cases was of especial interest, and it was desirable to discover, if possible, a difference from the normal ulcer cases. The complaint was practically the same, pain came on two to three hours after eating, and food and soda gave relief. The responses were very vague with regard to the location of the pain in any particular part of the abdomen. When these patients were asked whether or not the last operation helped them, all answered, "Yes." Twenty-two of the thirty-two were benefited by the operation, thirteen were symptomless, and nine had a few symptoms.

The question asking for voluntary information did not afford much data of value so far as the symptomatology of the gastrojejunal ulcer was concerned.

EXPERIMENTAL

The experimental part of the investigation was conducted mainly to attempt to determine whether the blood leaving the stomach is more alkaline than that coming into it. This part of the research was carried out on dogs under ether anesthesia. Three methods of procedure were tried:

1. The stomach was resected and suspended in normal saline solution kept at constant temperature. A cannula was inserted into the gastric artery and connected with a constant pressure apparatus. The perfusate was normal saline with as much of the dog's own blood as could be collected. The solution was kept at body temperature and perfused repeatedly through the stomach. It was soon discovered that such an experiment was unsatisfactory, owing principally to the great edema which developed after perfusion had continued for about half an hour. Under such conditions the gastric cells could not function normally. They were greatly swollen and the whole stomach wall was translucent.

2. It was thought that by using a heart-lung-stomach preparation the blood could be kept in circulation through the stomach and that the same blood could be made to pass through the stomach, many circuits in a unit of time, and each time increase the alkalinity. The arch of the aorta, and all the vessels leaving the thoracic and the abdominal aortas were ligated. Just below the celiac axis the abdominal aorta was ligated again. This, of course, necessitated opening the chest. A trachea cannula was inserted, and connected to a Connell apparatus. None of the animals lived long enough to permit an accurate test. They succumbed in less than an hour.

3. Finally the technic as follows was devised: A low tension of ether was maintained with a Connell apparatus. The chest was not opened. The circulation to the head and upper extremities and to the thorax was not disturbed. The circulation to the spleen, pancreas and intestines was stopped by double ligation and section. The abdominal aorta was ligated just above the superior mesenteric artery. All the venous radicals of the portal veins, except those draining the stomach, were ligated. This permitted the collection of venous blood from the portal vein, and thereby all the returned blood,

well mixed, from the stomach. The arterial blood was taken from the aorta.

The first few experiments were conducted after the animals had fasted from eight to eighteen hours. The animals did not show any appreciable increase in alkalinity of venous blood as compared with the arterial. The same experiments were performed with the stomachs full. The esophagus was ligated to keep the fluid in the stomach from drowning the animal. An increase in the alkalinity of the venous blood, both in its hydrogen ion concentration and its carbon dioxid combining point was shown. The carbon dioxid combining point, however, in all the experiments with venous and arterial blood, was lower than normal. The carbon dioxid combining point was estimated by the Van Slyke apparatus. The hydrogen ion concentration was estimated by the colorimeter method of Rowntree. The blood chlorid was estimated in some of the experiments.

A part of the experimental work was undertaken for the purpose of investigating more closely the autodigestion theory of ulcer production. There are two, perhaps three, phases to this theory, (1) the death of the mucosa cells, (2) the digestion of the cells, and (3) secondary infection. I was greatly impressed with the fact that on injecting solutions of stains into the gastric artery, the part of the stomach which is by far the greatest ulcer bearing area, takes stains much more deeply than other parts. The lesser curvature and the juxtapyloric region were much more deeply stained than the fundus and the greater curvature. This picture suggested the idea that ulcer production is related in some way to blood supply. The gastric cells are dependent on the blood supply for their vitality, and resistance to autodigestion. The elements which are supposed to prevent autodigestion are known as antiferments. Since the ferments are the cause of the digestion of the cells after their death, it seemed worth while to make a few investigations with regard to the biologic reactions and the commercial ferments. Rabbits were used in these experiments since ulcers are easily produced in them and they are easy to handle.

Three series of experiments were conducted, one with pepsin, one with trypsin, and one with peptone. Ten per cent solutions of these substances were made in a very weak tricresol solution. The rabbits were injected at weekly intervals for three weeks, they were then killed, necropsy was performed, and the blood tested. The initial dose of solution was 5 c.c., the second dose 7 c.c., and the third dose

10 c.c. Larger doses than these produced immediate death. The first injection was made intravenously into the ear, December 13, 1918, the last was made January 14, 1919. The stomachs of all the rabbits at necropsy were normal.

To test the blood for any increased antiferment power, artificial gastric juice was used (300 per cent acidity, and 0.016 mm. to 30 c.c. of pepsin). Two hundred millimeters of tissue were placed in wide mouthed bottles containing 30 c.c. of the artificial gastric juice. Five different kinds of tissue were selected, fundic, pyloric, jejunal, duodenal, and colonic. In each bottle were placed 5 c.c. of the fresh serum of the rabbits. As controls, another set of bottles without serum were used. The test bottles were placed in an incubator at body temperature for twenty-four hours, and then the amount of digestion was noted. There was no retardation of digestion in the bottles containing the serum of rabbits which had been injected with the ferments or the peptone. The different tissues did show variations in the amount of digestion. Kawamura in 1911 demonstrated this very definitely.

Dogs were used next in the ferment experiments. The dried ferments were not used, since in their preparation they might have been injured to an extent to destroy their power to produce a biologic reaction, if they had possessed it. Instead of injecting the ferments in solution intravenously, the major pancreatic duct was implanted into the splenic vein. This experiment was performed on four dogs, one January 9, one January 13, one January 15, and one January 17, 1919. In three of the animals the splenic vein was under considerable tension, and it was doubtful whether or not the pancreatic juice had run into it. The fourth operation was very successful from a technical point of view. In addition to the ferments, alkali was found to be a factor of especial interest. The blood chlorid was also studied in these dogs.

PROTOCOLS OF PANCREATIC DUCT EXPERIMENTS

Dog C945 Experiment 10: Blood Reactions

	Phenolsulphonephthalein, per cent	Carbon dioxid volumes per cent	Chlorin mg. per 100 c.c.
Jan. 13, 1919	7.4	30	500
Jan. 29, 1919	7.7	58	
Feb. 18, 1919	7.6	58	

The animal was a male, no catheter specimens of urine were obtained.

DOG C942 EXPERIMENT 11: BLOOD REACTIONS

	Phenolsulphonephthalein, per cent	Carbon dioxid volumes per cent	Chlorin mg. per 100 c.c.
Jan. 9, 1919	7.2	40	540
Jan. 10, 1919	7.5	38	485
Jan. 13, 1919	7.6	38	530
Jan. 17, 1919	7.5	48	530
Jan. 29, 1919	7.6	32	
Feb. 18, 1919	7.4	36	

The urine remained alkaline until January 20; there was a slight reduction of phenolsulphonephthalein solution for three days. The animal recovered from the operation.

DOG C946 EXPERIMENT 20: BLOOD REACTIONS

	Phenolsulphonephthalein, per cent	Carbon dioxid volumes per cent	Chlorin mg. per 100 c.c.
Jan 15, 1919	7.2	36	425
Jan. 17, 1919	7.5	38	
Jan. 29, 1919	7.3	42	

The dog was killed March 18, 1919. At necropsy the splenic vein could be found but it was completely thrombosed. In all probability the pancreatic juice had not passed through it.

DOG C958 EXPERIMENT 43: BLOOD REACTIONS

	Phenolsulphonephthalein, per cent	Carbon dioxid volumes per cent	Chlorin mg. per 100 c.c.
Jan. 20, 1919	7.4	..	625
Jan. 29, 1919	7.6	48	
Feb. 18, 1919	7.4	32	

The urine of this animal was examined repeatedly for alkalinity, but it was always acid.

Necropsy findings in the remaining animals were the same as those in the first. No ulcers were found. While no definite conclusions can be drawn from these experiments it would seem that the slight initial increase in the hydrogen ion concentration and carbon dioxid content show that for a time the pancreatic duct emptied into the vein. Further experiments will be carried out in which the duct will be inserted into a larger vein.

In a clinical review of the cases in which operations had been performed on the stomach, I emphasized the fact that when the acidity of the stomach was greatly lowered no gastrojejunal ulcers resulted. Such ulcers rarely form in a gastro-enterostomy performed for cancer. None were found in the series of 3,840 cases, either following resection for cancer or for multiple ulcers. These and other findings made it appear desirable to investigate the acid phase of the autodigestion theory of ulcer production.

Ulcer is produced only if the mucosa is acid, or at least if it is acid a greater part of the time. This is proved more or less by the position of such ulcers. They are either in the stomach or duodenum, and if a gastro-enterostomy is made they may occur in the jejunum. In one instance at the Clinic an ulcer was found in the ileum following a gastro-ileostomy made elsewhere. To assume that an ulcer is produced on acid mucosa, one must establish the fact that the first 2 inches of the duodenum is acid. This we tried to do, but not having the use of the fluoroscope at all times, our attempts were not faultless. This obstacle, however, was overcome and later experiments furnish more evidence of the exact position of the bucket and of the Rehfuss tube. Most of the duodenal ulcers are found less than 2 inches from the pyloric orifice, which, if we are correct in our inference that all ulcers are formed on an acid base, would indicate that this area is acid. Ulcers never occur low down in the duodenum, and very rarely in the afferent limb of the gastro-enterostomy.

Twenty patients have been examined. Four had normal gastro-intestinal tracts. Four showed no free acidity with the dimethylamidoazobenzol reagent. One with splenic anemia and one with gastric polyposis, in which more than one-half of the stomach had been resected, had no free acid in the stomach. Ten patients had duodenal ulcers; their histories and the x-ray findings were definite, and were proved by operation. In most of these cases fluoroscopic examination was made and in one or two plates were made. The duodenal contents were collected by a technician skilled in the work. The patients were fasted from the evening before. They were allowed water up to 11:00 a.m. Between 1:30 and 2:00 p.m. the Rehfuss tube was passed. Contents were collected from one-half hour to two hours later, depending on the time taken for the tube to enter the duodenum. The patients were then fluoroscoped, after which the contents were collected. In some instances the contents were collected before the patient was taken to the x-ray department. The tube remained in place from one and one-half hours to three hours

In all of the duodenal ulcer cases an acid reaction was shown with the bucket near the pylorus; if it was allowed to descend (not verified by roentgen ray), the contents became alkaline. In the normal cases acid was shown in ten, and alkali in two. In the cases in which there was no free hydrochloric in the stomach the reaction was alkaline. In the splenic anemia case, with a gastric analysis of 8 0–8 the reaction was alkaline also. In the case of gastric polyposis, with pylorectomy the reaction was alkaline.

There is a border-line or rather a neutralizing zone in the duodenum, the position of which depends on the relative acidity and alkalinity of the stomach and of the duodenum respectively. If the stomach manufactures more acid than the duodenum manufactures alkali, the zone is pushed distalward and vice versa. It is hoped that by collecting specimens, and at the same time keeping constant watch with the fluoroscope of the position of the bucket and by estimating the acidity of the stomach and the alkalinity of the duodenum, more detailed reports may be obtained.

The simplest theory of ulcer production may depend on acidity and alkalinity alone. The stomach has a method of its own to protect itself from over-acid cells, but so far as we know, the duodenum does not have this mechanism and a higher acid chyme acting on the duodenal cells for any length of time could kill them.

In order to test the time element of reaction an attempt was made to place the Rehfuss tube in the duodenum, and then instill into it 5 c.c. of 0.2 per cent hydrochloric acid solution. Small specimens were collected every fifteen minutes. In this manner the neutralizing power of the duodenal alkali was estimated on definite amounts of hydrochloric acid instilled. Twenty successful experiments were performed.

Beside the exogenous acidity relation there seems to be an endogenous relation. As has been stated, the stomach has its own method of protecting its mucosa.

The stomach produces acid throughout the day; the process of acid production is greatest after the ingestion of a meal, especially after a protein meal. Owing to the action of the gastric cells, the acid ion chlorin separates from its base, which we may quite safely assume is sodium, and leaves the body. Whether the sodium remains as hydroxid, or carbonate or acid carbonate is not known, nor does it make any material difference, since they are all alkaline. The stomach withdraws acid from the body in which the alkali remains; it therefore possesses a function with which it is not generally credited; it is an alkali manufacturer or alkali preserver, a kind of a solvay process in the human economy. To counterbalance this, other organs must form acid by removing alkali. This suggests another chain of acid-base equilibrium other than the carbon dioxid chain of the lungs, and the phosphate chain of the kidneys. The duodenectomy experiments of Mann and Kawamura show that the counterbalance is not due to the duodenum itself. The blood reaction in animals used for their experiments remained the same after the entire duodenum was removed. Thus the large digestive glands in its vicinity, the liver and pancreas, remain for investigation. All tissue metabolism leads to acid production, but not to actual removal of the alkali base. This process is associated with only inorganic acids and bases.

The organic acids produced by tissue metabolism have to be carried to their place of exit by the alkalies of the body. As chlorid (the great source of alkali for the body in the form of sodium chlorid), the base sodium is of no use to the tissues as a carbon dioxid carrier. It is only when the stomach takes off the chlorin radical that the alkali becomes of real use to the body for such purposes. The alkali reserved by the stomach not only protects its own cells from a hydrochloric acid death, but furnishes alkali to carry off the organic acid wastes of the body.

Protocols 1 and 2 are compiled from tests made on fasting dogs. The first one does not show anything of importance except the low carbon dioxid value. This low carbon dioxid value runs through the entire series, but the reason for this will not be discussed herein.

In Protocol 2 one may find some evidence of the increased alkalinity of the venous blood leaving the stomach. The manifestation is not so distinct as in some of the other protocols but more pronounced evidence was not expected from the fasting stomach.

Protocol 3 shows that 100 c.c. of 10 per cent peptone solution were placed in the stomach; it was hoped to stimulate the stomach to activity. Just before introducing the slightly alkaline peptone solution the dimethylamidoazobenzol test showed no free hydrochloric acid in the stomach contents of the animal used for this experiment. The acidity of the contents removed from the stomach at the end of the experimental period showed that some secretion of hydrochloric acid had taken place.

Protocols 4, 5, and 6 show the results obtained by feeding the animals two to three hours before beginning the experiment. The animals were fed meat, milk, and dog biscuit. The contents of the stomach were always acid after the experiment. The venous blood was more alkaline than the arterial blood and than the venous blood in the general circulation.

In the later experiments the venous blood of the general circulation was estimated by that taken from the external jugular vein. This was to detect any possible difference in the alkalinity of the return blood from the stomach and the blood in the general circulation.

PROTOCOLS OF TYPICAL GASTRIC EXPERIMENTS

Dog C928 Experiment 793

Dec. 20, 1918, 1:30 p.m.; blood pressure 120. Blood reaction

	Time	Phenolsulphonephthalein per cent	Carbon dioxid volumes per cent	Chlorin mg. per 100 c.c.	Blood pressure
Arterial	2:45	...	33	730	70
Venous	2:45	...	30	730	70
Arterial	3:45	...	29	740	
Venous	3:45	...	32	740	
Arterial	4:45	...	8	750	40
Venous	4:45	...	10	750	40

Dog C940

Jan. 8, 1919, 1:30 p.m.; blood pressure 145. Blood reaction

	Time	Phenolsulphonephthalein, per cent	Carbon dioxid volumes per cent	Chlorin mg. per 100 c.c.	Blood pressure
Arterial	3:00	7.1	10	540	80
Venous	3:00	7.6	8	465	80
Arterial	4:00	7.1	8	540	30
Venous	4:00	7.3	22	595	30

Dog 941

Jan. 9, 1919, 9:00 a.m.; blood pressure 100; blood reaction. 100 c.c. 10 per cent peptone solution placed in stomach; phenolsulphonephthalein 7.1 per cent.

	Time	Phenolsulphonephthalein, per cent	Carbon dioxid volumes per cent	Chlorin mg. per 100 c.c.	Blood pressure
Arterial	10:10	7.4	6	450	100
Venous	10:10	7.6	28	400	100
Arterial	11:40	7.2	10	450	20
Venous	11:40	7.3	22	440	20

Hydrogen ion concentration 6.8.

Dog 956

Jan. 16, 1919, 9:05 a.m.; blood reaction

	Time	Phenolsulphonephthalein, per cent	Carbon dioxid volumes per cent	Chlorin mg. per 100 c.c.
Arterial	9:55	7.45	10	575
Venous	9:55	7.9	18	565
Arterial	10:05	7.3	8	515
Venous	10:05	7.6	8	505
Heart	.....	7.3	12	

Gastric contents acid, hydrogen ion concentration 6.6.

Dog C967

Jan. 23, 1919, 8:55 a.m.; blood reaction

	Time	Phenolsulphonephthalein, per cent	Carbon dioxid volumes per cent
Arterial	9:56	7.3	8
Venous	9:56	7.5	38
Arterial	10:56	7.2	8
Venous	10:56	7.6	10
Heart	10:56	7.4	18

Gastric contents acid, hydrogen ion concentration 6.6.

Dog D4

Feb. 5, 1919, 10:00 a.m.; blood reaction

	Time	Phenolsulphonephthalein, per cent	Carbon dioxid volumes per cent
Arterial	11:20	7.35	28
Venous	11:20	7.50	39
Jugular	11:20	7.3	26
Arterial	12:20	7.45	10
Venous	12:20	7.55	18
Jugular	12:20	7.45	14
Arterial	1:40	7.2	10
Venous	1:40	7.25	14
Jugular	1:40	7.05	

Gastric contents acid, hydrogen ion concentration 6.6.

In the first series of experiments the blood chlorid was estimated in order to demonstrate whether a chlorid deficit was present. The results obtained suggest such a deficit. I should have liked to continue these estimations in all the bloods taken, but I found that the loss of sufficient blood for the tests was too great a shock to the animal. The operation in itself is very severe. This added element of blood removal lowers the blood pressure so much that the chlorid estimations were necessarily abandoned. By future work I hope to improve the technic to such a point that more blood can safely be removed.

SUMMARY

1. The stomach reserves alkali for the body.

2. The alkali has a two-fold purpose; it prevents the death of its own cells by guarding against overacidity; it replaces the alkali secreted by the kidney and pancreas, and thus keeps the body at a constant level of basic alkali, so that the acid waste products may be removed.

3. Peptic ulcer is always produced in an acid environment.

4. The first 2 inches of the duodenum are acid most of the time. In patients with duodenal ulcer they are probably acid all the time.

5. Most ulcers occur on the lesser curvature of the stomach because the blood is less alkalin when it first enters the stomach.

6. Food ease in duodenal ulcer is due to an increased alkalinity of duodenal cells.

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A STUDY OF THE ARTERIES SUPPLYING THE STOMACH AND DUODENUM AND THEIR RELATION TO ULCER*

THADDEUS B. REEVES

At operation practically all ulcers of the stomach are found along the lesser curvature. Ninety-eight per cent of the duodenal ulcers brought to operation at the Mayo Clinic are found within 1.5 inches of the pylorus; the greater number of these are on the anterior wall. In order to determine whether or not there is any difference between the character of the arteries which supply these regions of the stomach and duodenum and those which supply the remainder of the organ, sixty-two human stomachs obtained at necropsy were studied. Most of these had been injected with a mildly acid gelatin carmin solution prior to their removal.

The anatomy of the arteries supplying the stomach and the arteries to the gastric submucosa are described. A decided difference is noted between the arterial plexus of the submucosa of the lesser curvature and that of the submucosa of the remainder of the stomach. The arteries of the former are much smaller and almost twice as long as similar sized vessels in other parts of the stomach. The arteries of this region, however, have few anastomoses.

The submucous plexus gives off two systems of branches; one passes to the muscular coats, the other to the mucous coat. The system of vessels to the mucous coat is rather complicated; the arteries proceed in a slanting, tortuous, spiral course toward the muscularis mucosa. As the stomach becomes distended with food the tortuosity is lessened and a fuller blood supply to the mucous membrane is gained during the digestive activity. It is found, however, that there are two permanent folds, one along each side of the lesser curvature. These do not disappear on gastric distention.

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The first 1.5 inches of the duodenum receive their blood supply chiefly from the supraduodenal artery, which is given off by the gastroduodenal or hepatic artery. The submucosa of this part of the duodenum contains very few arteries in comparison with the other parts; this is especially notable on the anterior surface. These anatomic facts may explain the "anemic spot" described by W. J. Mayo, which is usually seen on the surface of the bowel in this region when the wall is put on tension.

Hematogenous infection has been considered by many investigators a potent etiologic factor in the production of gastric and duodenal ulcers. Virchow was among the first to point out that a thrombosis or other vascular lesion producing obstruction of the vessels in the gastric mucosa results in a hemorrhagic necrosis; this tends to cause the formation of ulcer in the presence of gastric juice. In the area of predeliction for ulcer formation the blood supply is not so free as in the other parts of the stomach, since the arteries are smaller and longer, and make fewer anastomoses. The fact that permanent folds along the lesser curvature of the stomach remain even during gastric distention tends to make the blood supply of the area relatively less than that of the remainder of the stomach during digestive activity. The small arteries of the submucosa of the first portion of the duodenum are comparatively few in number, they make few anastomoses, and similarly they predispose to circulatory disturbances which may lead to thrombosis. Therefore, since the vessels in these regions are liable to be occluded by emboli, it is reasonable to suppose that they are an important factor in the production of ulcer by hematogenous infection.

THE DEVELOPMENT OF THE LIVER AND PANCREAS IN AMBLYSTOMA*

EDWIN A. BAUMGARTNER

As a contribution to the knowledge of the morphology of the biliary and pancreatic duct system in vertebrates, the development of the biliary and pancreatic duct systems in typical amphibians was studied in detail with particular attention to the embryologic significance of their principal variations in the adult and to the mechanic influences which in part at least are responsible for them.

A series of about ninety sectioned specimens of embryos of *Amblystoma punctatum* varying in length from 4.5 mm. to 35 mm. was studied. Most of the earlier stages were studied by means of plastic reconstructions, the later stages by graphic reconstruction and dissection.

In Amblystoma the liver arises as a ventral projection of the lumen of the midgut into the anterior yolk-mass. This diverticulum is soon directed anteriorly and later, under the influence of the pressure of the developing stomach and duodenum, is shifted to the right and dorsally. The left lobe of the liver is formed at a later period as a secondary growth from the main mass of the organ.

The original anterior outgrowth from the midgut forms the ductus choledochus and this structure by growth and repeated divisions forms the right and left hepatic ducts and their rami and branches.

The gallbladder arises as a median ventral outpouching of the posterior part of the liver pouch. Like the liver it is soon shifted to the right through the growth and pressure of the duodenum and stomach. The stalk of the gallbladder forms the cystic duct which in early stages is attached to the ductus choledochus. But when the ductus choledochus divides into left and right hepatic ducts the cystic duct remains attached to the latter and is carried backward with it in the course of the left lobe of the liver. Eventually the cystic duct secures a secondary connection with the lateral ramus of the right hepatic duct.

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As in other amphibians, the pancreas of Amblystoma arises from three outpouchings, one from the dorsal and two from the ventral surface of the duodenum. Each of the ventral outpouchings give rise to a separate ductus choledochus or opens independently into the duodenum beside it. The dorsal pouch forms a single duct which always retains an independent opening into the duodenum.

The main mass of the adult pancreas is formed from the dorsal pancreatic outpouching while the ventral pouches form only a small portion of the lower extremity of the organ. The dorsal and ventral portions fuse together at an early stage of development but the connection between the two portions always remains as an attenuated band of tissue which can easily be recognized in the lower or ventral part of the gland.

MULTIPLE POLYPOSIS OF THE INTESTINAL TRACT*

JOHN E. STRUTHERS

A careful review of the literature on intestinal polyposis is presented and thirty-nine cases of this disease observed in the Mayo Clinic from January, 1911 to February, 1920 are studied with regard to etiology, pathology, symptoms, and other important data.

Multiple polyposis of the intestinal tract is a serious disease of obscure origin. Although all ages from adolescence to physiologic decline are affected, 37.5 per cent of cases occur in persons between 19 and 30. The number of cases in this series decreased progressively with the advance of years. The disease occurs more frequently in males than in females, the sex ratio being 2.9 to 1.0. The duration of symptoms ranged from three weeks to thirty-four years; 60 per cent of the patients had had symptoms for three years or more, while 54 per cent had had symptoms for five years or more.

The principal symptoms are sense of weight in the rectum, tenesmus, bleeding, diarrhea, vague abdominal pain, colics of obscure origin, partial obstruction, and essential hemorrhage. Essential hemorrhage is a nearly pathognomonic sign of this lesion. The rectum, the sigmoid, and the splenic and hepatic flexures are most frequently involved. Thirty-four of the thirty-nine patients had periods of diarrhea and thirty-one had abdominal pain at some time during the course of the disease. Rectal pain, bleeding, loss of weight, and so forth, were variable and at times due in part to coincident lesions, such as gastric ulcer, duodenal ulcer, and hemorrhoids. All except two patients had loss of weight ranging from 10 to 60 pounds. A study of the blood in twenty-nine cases showed a hemoglobin below 50 per cent in only one-fourth of the cases. Examination of the stools also contributed very little to the study. The value of proctoscopic examination is evidenced by the positive findings in twenty-eight cases.

Twenty-two of the series of patients were treated surgically by various types of operation, including the Brown operation, ileo-colostomy, colectomy, ileo-sigmoidostomy, the Mikulicz operation, the two-stage Kraske operation, appendicostomy, and the Desquin-Mixter operation. Nineteen of the patients treated surgically have been accounted for with a mortality of 47.34 per cent. Twelve of fourteen patients treated medically were heard from with a mortality of 25 per cent. In comparing these two groups of statistics it should be remembered that medical treatment afforded no possible hope for recovery in the patients who came to operation and that surgery gave them the only chance for life.

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The findings at operation and at necropsy indicate that multiple polyposis is a diffuse condition of the colon. The findings of Hewitt and Howard, that polyps in the rectum are situated along the side of the intestinal wall while higher up in the colon they are situated along the line of mesenteric attachment, have not been confirmed in the Mayo Clinic.

Schwab's theory of chronic constipation in the etiology of the lesion is hardly tenable in view of the prevalence of polyposis in males and the high incidence of chronic constipation in the female. Proctoscopic examination of patients and microscopic examination of specimens removed at operation frequently show ulceration associated with polyposis and tends to confirm Rokitansky's theory that intestinal polyps arise from the margins of dysenteric ulcers.

According to the pathology intestinal neoplasms are classified as papillomas, polyps, and adenomas, the latter predominating (40 per cent). In a large percentage of cases there is a progressive general colitis which forms a number of undermining coalescing ulcers so that large areas become involved. Portions of the mucosa and submucosa supplied by primary arterial branches are preserved and as healing takes place the irregular margins of these elevations are smoothed off and remain as polypoid projections. Subsequent cicatrization may occlude the tubules while continued functioning of the secreting cells results in small retention cysts. Friction and traction on these elevated areas cause pedicles. Further inflammatory or degenerative changes may occur. Adenomas do not become malignant more frequently than polyps or papillomas. The most marked involvement is found in the chronic cases and, conversely, the area involved is most localized in the acute cases.

TORSION OF APPENDICES EPIPLOICÆ*

VERNE C. HUNT

The appendices epiploicæ appear along the entire large intestine except the rectum. Their shape and size are variable, depending on their content. Their function has not been determined.

The pathologic changes incident to the appendices epiploicæ are usually those attending mechanical interference with the blood supply. A number of cases have been reported in which torsion of an appendix epiploica occurred in a hernial sac. Fat necrosis is the chief degenerative change, and is often associated with considerable inflammatory reaction. Subperitoneal hemorrhagic effusions occur, and at times only small ecchymotic areas with dark discoloration are seen. Direct microbic invasion of appendices epiploicæ from the lumen of the bowel seems a very probable etiologic factor in their disturbances. Torsion of an appendix epiploica intra-abdominally may suddenly deprive it of its circulation and necrosis occur so rapidly that it drops off and remains in the peritoneal cavity as a free body. Such foreign bodies have been found in four cadavers and in seven instances at operation.

The forty-two cases recorded in the literature under the combined titles of "torsion and inflammation of appendices epiploicæ" are abstracted. Nineteen were true cases of torsion, nine of which were cases of torsion within the abdomen and ten within a hernial sac. The intra-abdominal cases presented symptoms of acute lesions simulating acute appendicitis, intestinal obstruction, gallbladder disease, and so forth. The cases in which torsion occurred within a hernial sac presented the acute symptoms of strangulation or incarceration of the hernial contents. In thirty of the forty-two cases in the literature the symptoms were of sufficient severity to require urgent surgical interference.

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To the cases of torsion of an appendix epiploica reported in the literature the author adds abstracts and a discussion of the eleven cases observed in the Mayo Clinic from January 1, 1908, to January 1, 1918. Seven of these were cases of true torsion, one of doubtful torsion, two of incarceration in an inguinal hernia, and one of a foreign body in the peritoneal cavity. Four of the true cases of torsion presented acute symptoms for which operation was performed; in the remaining three cases the condition was probably symptomless, since it was found in the course of abdominal operations for other pathologic conditions. The cases in which torsion occurred within a hernial sac presented symptoms of incarceration of the hernial contents.

The cases from the literature and those from the Mayo Clinic indicate that the symptoms may vary greatly in degrees of severity and may mimic any of the truly acute organic lesions of the abdomen. In the combined series of cases the appendices epiploicæ of the sigmoid were the most frequent source of torsion and inflammation (twenty-eight cases); in six cases, however, the origin of the appendix was in the cecum, and in one in the transverse colon. Because of the close proximity of the sigmoid to the left internal inguinal ring, left inguinal hernias are more likely to contain appendices epiploicæ than right inguinal hernias, and in the twenty-four cases in which torsion or strangulation of an appendix epiploica occurred in a hernial sac it was in a left inguinal hernia in seventeen cases, in a right inguinal hernia in five cases, and in a left femoral hernia in two cases. The amount of torsion of the appendices varied from one turn through 180 degrees to ten half turns. In the twenty-four cases of the combined series in which the age was stated, the youngest patient was 21, and the oldest 72.

CLINICAL STUDIES IN ABDOMINAL DISORDERS*

EGERTON L. CRISPIN

I. VISCERAL CRISES IN ANGIONEUROTIC EDEMA

The diagnostic importance of visceral crises is discussed more from the standpoint of value in negativing or avoiding surgery which does not give relief than from the standpoint of too closely differentiating inter-related medical conditions. When a history of severe abdominal pain is given which does not conform to true surgical types, careful inquiry should be made of the presence at any time of urticarias, erythemas, purpuras, or swellings of angioneurotic type. It is probable that most of these allied conditions, have, as an underlying condition, an angioneurosis. Some may be caused by chemical irritation, others may be of toxic origin, and many may have anaphylaxis as a basic cause. In all of this group localized vascular dilatation occurs and is associated with a serous or hemorrhagic exudation. The indefiniteness of the abdominal pains is of greatest diagnostic importance. A so-called neurotic tendency is often noted in the patient. There is no regularity to the return of pain nor is there a food-time relation. The location of pain is usually in the median abdomen.

Attacks usually last from four to six or eight hours. Visceral crises of this type are caused by the result of vasomotor changes and sufficient time must elapse for exudation to reach the painful stage and likewise for its disappearance.

The swelling in the viscera is analogous to that in the skin. Distention of the visceral coats following exudation of serum causes pain and if the pain is sufficient to cause pseudo-obstruction of the intestines, it is peristaltic. Blood may exudate into the stomach and if vomited, a diagnosis of ulcer may be made. Sometimes in cases of swelling of the right lower abdomen suggesting appendiceal abscess, only induration in the cecum and in the appendix is found at operation;

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* Abstract of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine, 1917.

the appendix is not sufficiently changed to be the primary cause of the condition.

Patients in the angioneurotic group with visceral crises have repeated attacks, sometimes for years, that cause great discomfort. In this group there seems to be no permanent visceral lesion for which surgery could give relief. A careful history and a more thorough physical examination will often help to clear up a diagnosis from a surgical-medical point of view.

The sources of toxemias, such as foci of pus in the upper respiratory tract and sinuses, idiosyncracies to heat, cold, chemicals or proteins that are the causes for anaphylaxis should be worked out. Removing the causes for anaphylaxis may give the patient the relief that surgery would not give.

II. TOXIC GASTRIC HEMORRHAGE

Attention is drawn to the fact that hematemesis does not always mean ulcer of the stomach, nor does it always warrant surgical interference. The differential diagnosis of hemorrhage due to chronic ulcer and hemorrhage due to nonsurgical conditions rests with the internist. Blood from the lungs and pharynx may be swallowed and later vomited; esophageal varices may bleed; and the purpuras, anemias, and leukemias may cause severe bleeding from the stomach. Young women may have extensive hemorrhage with no proof of chronic ulcer and usually with spontaneous recovery.

Rosenow has shown that the association of various streptococcic infections with multiple hemorrhage points in the gastric mucosa. Deaver, in discussing gastric bleeding not associated with ulcer, states his belief that the congestion of the gastric vessels is usually dependent primarily on an intra-abdominal, or, more rarely, remote focus of infection, usually the appendix or gallbladder.

Multiple mucous ulcers when secondary to infection elsewhere may not be palpable and may give negative roentgenographic findings. Chronic gastric and duodenal ulcers as a rule do not bleed copiously.

In general, surgery offers the best results for ulcer of the chronic calloused type. In this condition the patient goes to the physician because of distress from the ulcer rather than because of hemorrhage. In a second group of patients with gastric hemorrhage greater emphasis is given to the bleeding and to gastric symptoms that are more or less indefinite. In a third group are patients who come for treatment because of hemorrhages and who have minor gastric symptoms.

In cases of hemorrhage without gastric symptoms the condition should be considered toxic. Medical observation will further develop the exact nature of many hemorrhages of the toxic group and relegate them to their proper sphere. Correction, when possible, of the underlying conditions, and waiting, rather than surgery, is advisable.

Histories are reported in abstract to illustrate various types of gastric hemorrhages.

III. DUODENAL ULCER WITH ACHLORHYDRIA

In duodenal ulcer the total and free acids are usually high; however subnormal acidities are occasionally recorded. In gallbladder disease subacidity is quite common.

Eleven cases from the Mayo Clinic of operatively proved duodenal ulcer with absence of free hydrochloric acid are reviewed. The average duration of gastric disorder was six and nine-tenths years. All the patients gave a history of pain or distress either in the stomach, right or left epigastrium or back, varying from a dull aching to a burning, gnawing pain lasting until food was taken. The time of pain varied, beginning from one-half to four hours after meals. No free hydrochloric acid was found in the gastric contents. The acidity varied from 4-0-4 to 38-0-38, averaging 15-0-15. Gastro-enterostomy was performed in all cases and in five the appendix was removed.

Part I of this thesis is published in full in the St. Paul Medical Journal, 1916, xviii, 127–133;

Part II is published in full in the California State Medical Journal, 1916, xiv, 127–133;

Part III is published in full in the Interstate Medical Journal, 1916, xxiii, 890–891.

II

UROGENITAL ORGANS

THE EFFECT ON THE KIDNEY OF VARIOUS SURGICAL PROCEDURES ON THE BLOOD SUPPLY, CAPSULE, AND ON THE URETERS*

STUART W. HARRINGTON

This experimental study on the kidney and ureter was undertaken to determine the effect produced on them by some of the common surgical procedures or by accidents to them during operations on other organs.

The problems studied have been classified into four series, and the phases investigated have been arranged in groups.

Series I.—The effect on the kidney and ureter of complete sudden occlusion of the ureter or of complete sudden occlusion of the ureter and the collateral venous circulation.

Group 1. Double ligation and section of the ureter twenty-two experiments).

Group 2. Double ligation and section of one ureter and the collateral venous circulation (thirty-one experiments).

Series II.—The effect of occlusion of the various vascular radicals of the kidney.

Group 1. Ligation of the renal artery (five experiments).

Group 2. Ligation of one or more branches of the renal artery (sixteen experiments).

Group 3. Ligation of the renal vein (eight experiments).

Group 4. Ligation of one of the larger branches of the renal vein (two experiments).

Series III.—The effect on the kidney and ureter of trauma to the ureter.

Group 1. Clamping of the ureter (eleven experiments).

Group 2. Stripping of the ureter (six experiments).

Group 3. Anastomosis of the ureters (twenty-two experiments).

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Series IV.—The effect of decapsulation of the kidney.

Group 1. Decapsulation of the kidney and wrapping it in omentum (thirteen experiments).

Group 2. Decapsulation of the kidney and wrapping it in omentum after ligation of the renal artery or branches of the renal artery (seven experiments).

METHOD OF EXPERIMENTATION

Dogs were used in all the experiments because of the similarity of the anatomy, and particularly of the physiology and blood supply to those of man. Each surgical procedure was carried out with the strictest observance of aseptic technic identical with that used on man. The dogs were anesthetized with ether, the abdomen shaved, and thoroughly cleansed with alcohol and benzin and two applications of 10 per cent iodin. A straight upper right rectus incision was made in order to permit abdominal exploration and transperitoneal exploration of both kidneys and ureters. In many instances surgical procedures other than those on the kidney and ureter, such as gastro-enterostomy, partial resection of the stomach, cholecystectomy, fat transplantations, and so forth, were carried out in the study of other problems, but, in no instance was a procedure undertaken which would influence the results of the problem at hand. The technic of the various surgical procedures is discussed briefly under each series of experiments. The peritoneum and fascia were closed with catgut and the skin with linen. The wound was sealed with collodion. The dogs were kept under the most favorable conditions for health.

SERIES I. THE EFFECT ON THE KIDNEY AND URETER OF COMPLETE SUDDEN OCCLUSION OF THE URETER OR COMPLETE SUDDEN OCCLUSION OF THE URETER AND THE COLLATERAL VENOUS CIRCULATION

The first problem investigated was the effect produced on the kidney by sudden complete occlusion of the ureter and the factors concerned in the end results. This problem has a practical significance as it is frequently necessary to ligate one of the ureters during the course of various surgical procedures on man, such as the removal of a malignant growth of the bladder or pelvis when it is impossible or does not seem advisable to make other disposition of the ureter. The ureter has been ligated almost with impunity in man although many textbooks of surgery differ as to the effect produced on the kidney.

Watson and Cunningham state that complete total obstruction of the ureter does not cause hydronephrosis. Morris states that sudden complete stoppage of the outflow of urine leads to rapid atrophy and ultimate disappearance of the affected kidney. Keyes states that sudden complete obstruction of the ureter causes damming back of the urine on the kidney with acute renal congestion and a diminished secretion of the urine, and that this causes an increased intrarenal pressure. The congestion is exchanged for atrophy. Adami and Nicholls state that complete obstruction to the outflow of urine leads to atrophy of the affected kidney.

Group 1. Double ligation and section of the ureter (twenty-two experiments.—In this group of experiments the operative procedure was practically the same. The appearance and relative size of the kidneys and ureters were determined by transperitoneal exploration; the intestines were packed off and the lower third of the ureter exposed. If one ureter was normal it was doubly ligated with linen and sectioned, then replaced behind the peritoneum (eighteen experiments). In two experiments the ureter was doubly ligated with catgut and sectioned. In two the ureter was ligated with catgut but not sectioned in order to demonstrate the necessity of using permanent suture material to tie off the ureter when complete occlusion is desired. The animals recovered immediately from operation, and their general health during the experiments was good. Eleven of the dogs were sacrificed at desired intervals; five of the remaining nine died of distemper, two of sepsis from other operative procedures, and two of accident. A complete necropsy was made on each animal (Table 1 and Figs. 17 to 24).

The primary effect on the kidney, resulting from ligation of the ureter, is shown in Experiment 20. There was a marked congestion and edema from the increased intrarenal pressure which partially obstructed the venous return by compression of the smaller capillaries. This pressure was at its maximum in about twenty-four hours and gradually decreased with the duration of the obstruction. Rosow found an intrarenal pressure of 90 mm. in twenty-four hours, and of 6 mm. at the end of 279 days. The increased pressure soon produced a dilatation of the pelvis and ureter. The sequence of events was very regular but not uniform in all the animals with the same duration of obstruction.

Table 1.—Series I. The Effect on the Kidney and Ureter of Complete Sudden Occlusion of the Ureter or of the Collateral Venous Circulation

Group 1.—Double ligation and section of the ureter (Twenty-two experiments).

	Experiment	Animal	Date of operation	Duration of experiment, days	Ureter ligated	Necropsy	Pyonephrosis	Hydronephrosis	Dilatation of capsular veins	Condition of kidney not operated on	Reoperation; contents of sac removed	Sac refilled
1	(723)	B678	12–23–16	447	Right	121		Large	+	Hypertrophic		
2	(566)	C 95	8–10–17	217	Right	119		Large	+	Hypertrophic		
3	(43)	B732	1–20–17	153	Right	386		Large	+	Normal		
4	(290)	B901	3–26–17	102	Right	407		Large	+	Normal		
5	(724)	B655	12–23–16	47	Right	54		Large	+	Normal		
6	(727)	B679	12–23–16	40	Right	38		Large	+	Hypertrophic	1–12–17	+
7	(31)	B720	1– 3–17	28	Left	62		Large	+	Normal	1–17–18	+
8	(97)	B767	2–10–17	20	Left	105		Large	+	Normal	2–17–17	+
					Plain Catgut							
9	(631)	C136	9–10–17	16	Right	530	+	Moderate	+	Normal		
10	(17)	B706	1– 9–17	13	Left	16		Moderate	+	Normal		
11	(436)	C 12	6– 4–17	12	Right	377		Moderate	+	Normal		
					Plain Catgut							
12	(592)	C115	8–24–17	11	Right	506		Moderate	+	Normal		
13	(51)	B740	1–27–17	10	Left	50		Moderate	+	Hypertrophic		
14	(18)	B707	1– 9–17	9	Left	15		Moderate	+	Normal		
15	(14)	B703	1– 6–17	7	Left	13		Small	+	Normal		
16	(442)	C 18	6– 8–17	6	Right	370		Small	+	Hypertrophic		
17	(619)	C129	8–31–17	4	Right	511		Dilatation of pelvis and ureter	+	Normal		
18	(725)	B528	12–23–16	3	Right	577			+	Normal		
19	(284)	B872	3–17–17	3	Left	154			+	Normal		
20	(726)	B600	12–23–16	1	Right Plain Catgut	576		Congestion and edema of entire kidney	+	Normal*		
21**	(252)	B874	3–17–17	223	Left	49		Ureter normal		Normal*		
					Plain Catgut			Ureter partially constricted				
22**	(250)	B873	3–17–17	239	Left	48		Slight atrophy of kidney		Normal		

** Ligation without section.

* Kidney operated on normal also.

The increased intrarenal pressure produced by obstruction to the outflow of urine next caused a dilatation of the pelvis of the kidney, a flattening of the renal papillae, and compression of the medulla. This process was well-marked in seventy-two hours (Fig. 17). It was progressive and fairly uniform in the sequence with which the portions of the kidney were affected. First there was a definite

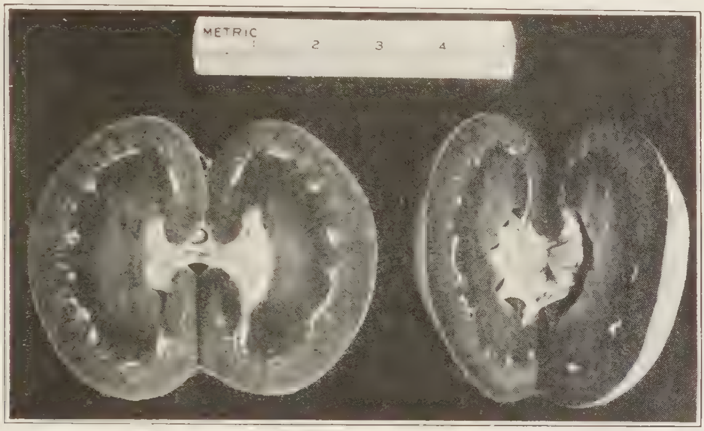

Fig. 17 (Series I, Group 1, Experiment 18 [B 528]).—Ligation of the ureter, three days' duration; beginning hydronephrosis, flattening of the renal papillae with depression and narrowing of the medulla.

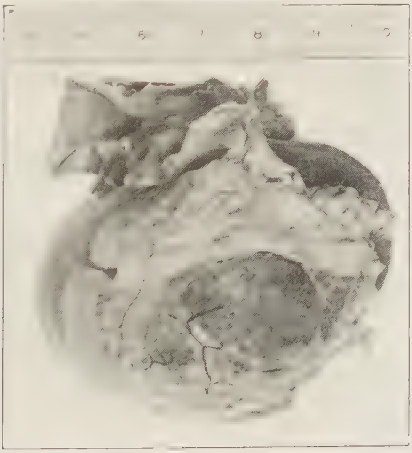

Fig. 18 (Series I, Group 1, Experiment 8 [B 767]).—Ligation of the ureter, twenty days' duration; hydronephrosis; marked dilatation of the capsular vessels over the surface of the hydronephrotic sac.

thinning of the renal parenchyma in the lateral portions of the kidney within ten days. The poles were next involved, showing a rather marked change in from fourteen to eighteen days. The median sagittal portion was the most resistant and at twenty-one days considerable renal parenchyma remained (Figs. 18 and 19), while at four

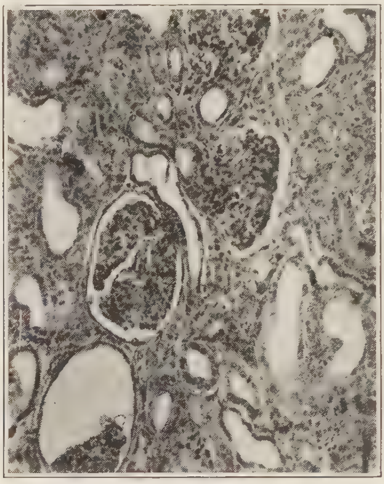

Fig. 19 (Series I, Group 1, Experiment 8 [B 767]).—Marked dilatation of the renal tubules and degeneration of the renal parenchyma of kidney shown in Figure 18.

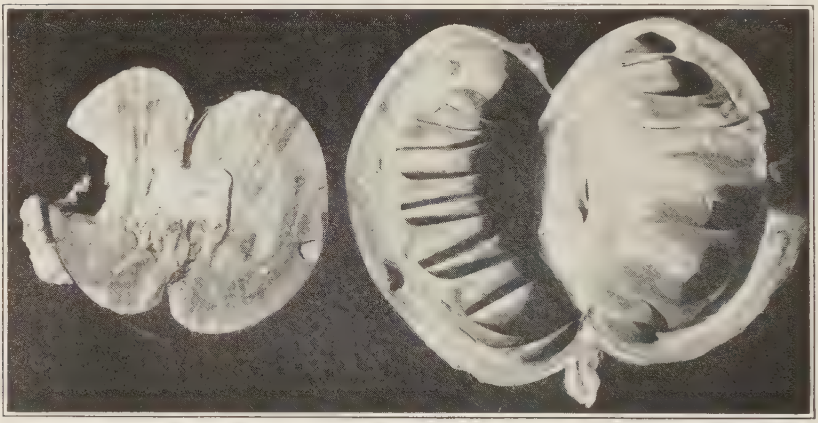

Fig. 20 (Series I, Group 1, Experiment 7 [B 720]).—Ligation of the ureter, twenty-eight days' duration; hydronephrosis; marked destruction of the renal parenchyma in the lateral portions, considerable tissue remaining in the median sagittal portion.

weeks or more only a very thin layer of renal parenchyma in scattered patches lining the sac remained. The interior of the kidney was partitioned off by columns of fibrous tissue radiating in a fan-like arrangement from the ureteral outlet (Fig. 20). These bands or columns contained the blood vessels which with their fibrous sheaths were relatively unaffected by the intrarenal pressure that caused

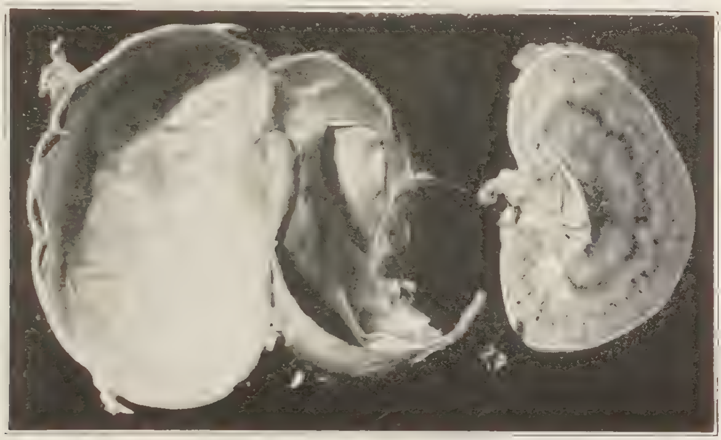

Fig. 21 (Series I, Group 1, Experiment 4 [B 901]).—Ligation of the ureter, 102 days' duration; complete destruction of the renal parenchyma; large monolocular hydronephrotic sac.

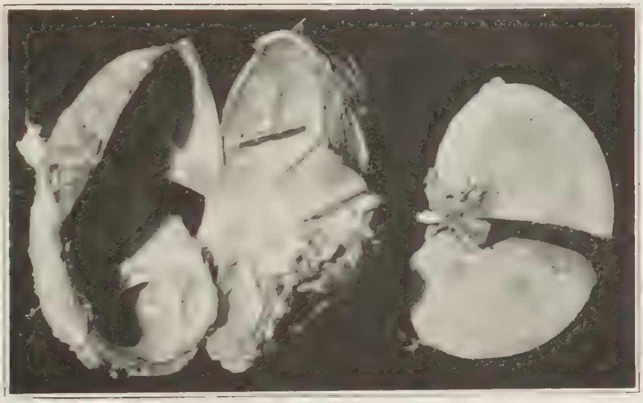

Fig. 22 (Series I, Group 1, Experiment 3 [B 732]).—Ligation of the ureter, 153 days' duration; complete destruction of the renal parenchyma; connective tissue bands radiating from the pelvis.

atrophy of the renal parenchyma lying between them. These bands of fibrous tissue caused the lobulated appearance of the surface of the kidney. The renal vessels could be seen running through the lobular grooves.

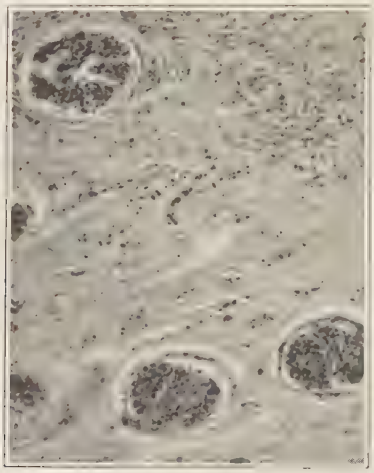

FIG. 23 (Series I, Group 1, Experiment 3 [B 732]).—Marked atrophy of the renal parenchyma of kidney shown in Figure 22; glomeruli fairly well preserved.

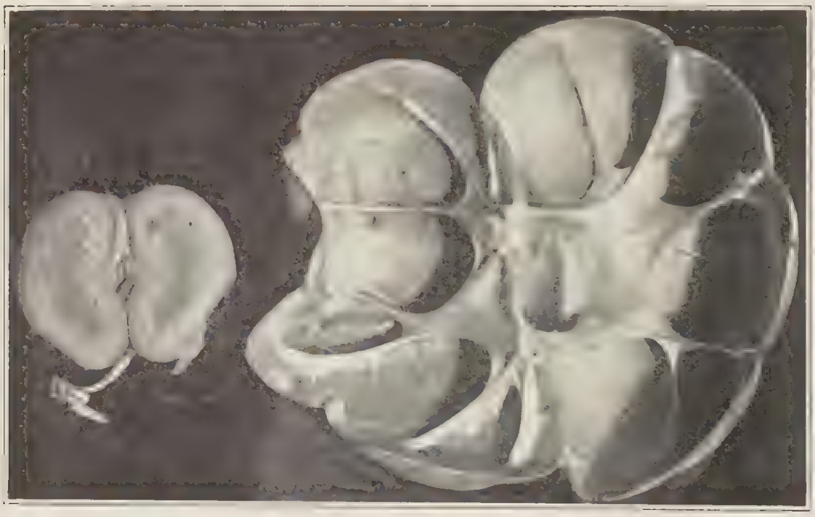

FIG. 24 (Series I, Group 1, Experiment 1 [B 676]).—Ligation of the ureter, 447 days' duration; enormous lobulated hydronephrotic sac; loculations due to connective tissue septums; complete destruction of the renal parenchyma.

The pelvis and ureter were markedly dilated and the capsular veins, radiating from the pelvis and passing over the surface of the sac were simularly dilated. The degree of dilatation of these veins seemed to depend on the amount of hydronephrosis. The changes in the renal parenchyma followed the same progressive course as the gross changes. The entire tubule (most marked in the collecting tubule and Bowman's capsule) was dilated and the convoluted tubule and the loop of Henle were compressed. Atrophy was noted first in the convoluted tubules, but was soon followed by the same process in all the tubular structures. The glomerular tufts, like the larger blood-vessels in the medulla, were much more resistant than the renal parenchyma and remained for a long time after the tubular structure had disappeared (Figs. 22 and 23).

In Experiment 6 a kidney which had been obstructed for twenty-one days had the power to secrete urine. The dog was reoperated on the twenty-first day and the contents of the hydronephrotic sac removed. The sac was found refilled with fluid when the dog was sacrificed on the fortieth day. In Experiments 7 and 8 the hydronephrotic sacs were evacuated on the fourteenth and seventh days respectively after the ureteral ligation. The sacs had refilled when the dogs were sacrificed on the twenty-eighth and twentieth days respectively.

The contents of the hydronephrotic sacs were acid in reaction with a fairly constant specific gravity, ranging from 1008 to 1010. The fluid contained albumin and urea, and usually sediment containing blood, probably the result of the early congestion of the kidney. In one experiment at necropsy a marked infection (pyonephrosis) was present.

In Experiments 1 and 12 the ureters were ligated with No. 1 plain catgut. In Experiment 1 the dog died on the sixteenth day from peritonitis from leakage of the ureter; a pyonephrosis had developed in the kidney (Fig. 24). In Experiment 12 the dog was sacrificed the eleventh day. The capsular veins were dilated and the ureter and pelvis enlarged but collapsed, showing evidence of a previous hydronephrosis; the contents of the sac had leaked out through the ureter. In both of these experiments the catgut ligature had been absorbed with leakage of the contents of the hydronephrotic sac. In Experiments 21 and 22 the ureters were ligated with No. 1 plain catgut but not sectioned. In Experiment 21, the dog died 223 days after operation. On examination of the ureter the site of the catgut ligature could not be found. There was no dilatation of the ureter and the kidney was normal. In Experiment 22 the dog was sacrificed in 239 days because of an infection resulting from another operation. On the examination of the ureter a slight constriction was found at the point of ligation with some dilatation of the ureter and pelvis about the constriction. The kidney was slightly atrophied; it weighed 33 gm.; the opposite kidney weighed 37 gm.

Experiments 21 and 22 show the necessity of using permanent ligating material when complete obstruction of the ureter is desired, since absorbable ligatures may produce only partial constriction and atrophy of the kidney ensue.

The experiments on this group of dogs conclusively show:

1. Sudden complete occlusion of the ureter produces a hydronephrosis in every instance, the degree depending on the duration of the obstruction.

2. The hydronephrotic cavity is developed by dilatation of the pelvis and atrophy of the renal parenchyma and of the walls of the kidney.

3. The atrophic changes are quite uniform in distribution but vary in different animals.

4. The kidney is capable of secreting after thirty-six days of complete ureteral obstruction.

5. The renal blood vessels are the last structures to be affected by the increased intrarenal pressure.

6. In every instance the capsular veins are dilated, the enlargement depending on the amount of hydronephrosis.

Group 2. Double ligation and section of one ureter and the collateral venous circulation (thirty-one experiments).—The consistency with which dilatation of the capsular veins accompanied hydronephrosis led to the experiments in Group 2.

The collateral veins are ordinarily too small to be noticed in the normal kidney. The dilatation of these veins during the development of hydronephrosis and the observation that their enlargement seems to be dependent on the amount of renal distention brought up the question of whether they were one of the causative factors in the production of the hydronephrosis or whether they were the result of the hydronephrosis. In order to determine the point, the capsular blood supply was ligated at the same time as the ureter. Tuffier and Lejars, working on the collateral circulation, ligated the renal vein and found that the renal venous blood is returned to the general circulation by four routes, (1) the inferior diaphragmatic and suprarenal vessels, (2) ureteric and spermatic vessels, (3) subcutaneous plexus of the lumbar region, and (4) the plexus which surrounds the last intercostal nerve, the ilio-inguinal nerve and the iliohypogastric nerve.

The technic of the operative procedure in Group 2 differed from that in Group 1 in that after the collateral circulation was carefully dissected out and the ureter freed, both were doubly ligated and sectioned so that the only blood entering or leaving the kidney was that which passed through the renal artery and vein. A definite hydronephrosis was produced in each instance and its progress was essentially the same as those in Group 1 except that it developed more slowly and to a less degree than when the collateral circulation was left intact. Frequently the kidney and its hydronephrotic sac were found to be smaller than the opposite normal kidney, in spite of the distinct hydronephrotic cavity produced by the progressive atrophy of the renal parenchyma (Table 2 and Figs. 25 to 38).

In Experiments 1 and 4, of 453 and 297 days' obstruction respectively, the hydronephrotic sacs were the largest in the group, but not so large as those in Group 1 in which the ureter alone was ligated. In Experiment 4, of 297 days' obstruction, the animal developed the largest hydronephrotic sac of the series. The kidney weighed 540 gm., and the sac contained 250 c.c. of purulent fluid. There were many adhesions about the kidney. In Experiment 1, of 453 days' ureteral obstruction, the kidney weighed 382 gm., and the sac contained 190 c.c. of clear fluid. The capsular vessels were not dilated.

In Experiments 2 and 3, of 422 and 337 days' duration respectively, a moderate degree of hydronephrosis developed, the sacs containing 40 c.c. and 30 c.c. of fluid respectively. No dilatation of the capsular vessels could be detected. In Experiment 2 the hydronephrotic kidney was smaller than the opposite normal kidney (Figs. 37 and 38). The parenchyma was completely destroyed.

In Experiment 15 the animal appeared to be in good health the night of the thirty-second day but was found dead the next morning. At necropsy the cause of death was found to be the rupture of a large pyonephrotic sac which had produced a peritonitis. Many adhesions were found about the sac.

Table 2.—Series I. The Effect on the Kidney and Ureter of Complete Sudden Occlusion of the Ureter or of the Collateral Venous Circulation

Group 2.—Double ligation and section of one ureter and the collateral circulation (thirty-one experiments).

	Experiment	Animal	Date of operation	Duration of experiment, days	Ureter ligated	Necropsy	Pyonephrosis	Hydronephrosis	Adhesions around kidney operated on	Condition of kidney not operated on
1	(581)	C697	8–12–18	453	Left	530	....	Large	0	Normal
2	(636)	C730	8–26–18	422	Left	493	....	Moderate	0	Normal
3	(35)	B724	1–13–17	337	Left	658	....	Moderate	+	Hypertrophic
4	(34)	B723	1–13–17	297	Left	592	+	Large	+	Hypertrophic
5	(430)	C 6	5–28–17	217	Right	677	....	Moderate	+	Hypertrophic
6	(582)	C106	8–28–17	200	Left	105	+	Large	+	Hypertrophic
7	(40)	B729	1–20–17	159	Left	396	....	Large	Omentum	Normal
8	(421)	B997	5–25–17	150	Right	555	....	Large	0	Normal
9	(32)	B721	1–13–17	149	Left	363	....	Large	0	Normal
10	(637)	C731	8–26–18	115	Left	702	....	Large	Omentum	Hypertrophic
11	(435)	C 11	6– 1–17	68	Right	462	+	Large	+	Normal
12	(422)	B996	5–25–17	59	Right	436	....	Moderate	0	Normal
13	(410)	B990	5–14–17	35	Right	380	....	Moderate	0	Normal
14	(580)	C104	8–20–17	34	Left	527	+	Moderate	+	Normal
15	(563)	C 92	8–10–17	32	Left	518	Ruptured	Large	Omentum	Normal
16	(522)	C 70	6–27–17	27	Left	475		Moderate	Omentum	Normal
17	(33)	B722	1– 3–17	24	Left	52	....	Large	0	Hypertrophic
18	(483)	C608	7–15–18	23	Left	428	....	Moderate	0	Normal
19	(20)	B709	1– 9–17	23	Left	37	....	Large	+	Normal
20	(525)	C 72	7–27–17	22	Left	490	....	Large	0	Normal
21	(420)	B996	5–25–17	19	Right	368	....	Moderate	+	Normal
22	(41)	B730	1–20–17	17	Left	51	....	Moderate	0	Normal
23	(502)	C627	7-22–18	17	Left	434	....	Small	0	Normal
24	(19)	B708	1– 9–17	16	Left	40	....	Small	+	Normal
25	(411)	B991	5–14–17	10	Right	336	....	Small	+	Normal
26	(545)	C666	8– 5–18	10	Right	457	....	Small	0	Normal
27	(545)	C 84	8– 3–17	9	Left	468	....	Small	0	Normal
28	(522)	C646	7–29–17	8	Left	419	....	Small	0	Normal
29	(580)	C696	8–12–18	5	Right	463	....	Small	Omentum	Normal
30	(722)	C161	10–26–17	5	Right	582	....	Small	0	Normal
31	(503)	C628	7–22–18	4	Left	393	....	Small	0	Normal

The animals in Experiments 4, 6, 11, 14, and 15 also developed pyonephrosis in the kidney operated on, which makes its incidence much higher in Group 2 than in Group 1, in which the collateral circulation was not interfered with.

In many of the animals there were adhesions of the omentum and of the structures adjacent to the kidney operated on, but not sufficient to have any bearing on the blood supply of the kidney.

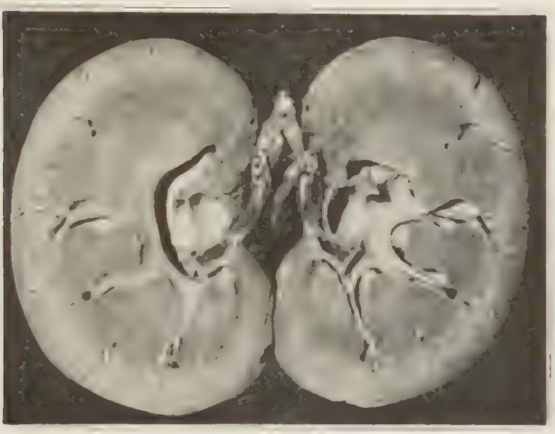

Fig. 25 (Series I, Group 1, Experiment 29 [C 696]).—Ligation of the ureter and collateral blood supply, five days' duration; small hydronephrosis; flattening of the renal papillae and thinning of the medulla.

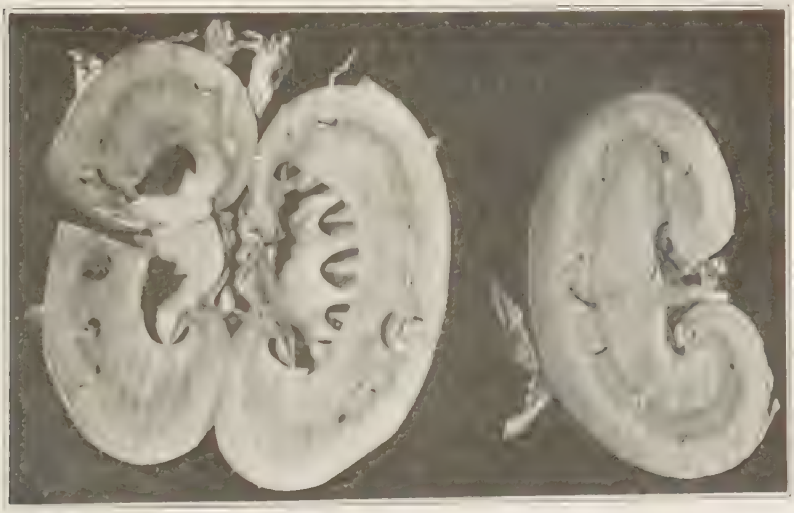

Fig. 26 (Series I, Group 1, Experiment 25 [B 991]).—Ligation of the ureter and the collateral blood supply, ten days' duration; small hydronephrosis; destruction of renal parenchyma in lateral portions, median sagittal portion still preserved; opposite kidney normal.

From these experiments conclusions as follows may be drawn:

1. Hydronephrosis develops in the kidney of a dog following the ligation of one ureter and of the collateral blood supply.

2. The hydronephrotic sac is smaller and develops more slowly if the collateral circulation is intact.

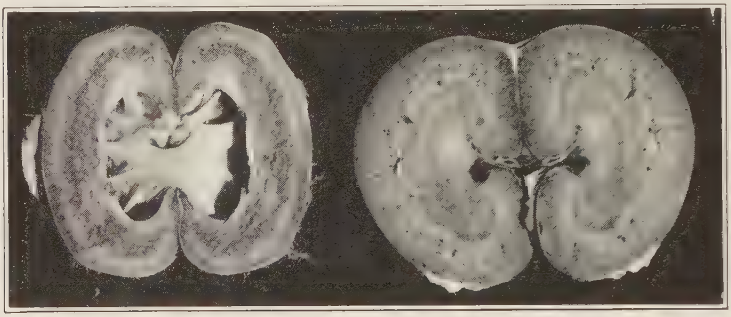

Fig. 27 (Series I, Group 2, Experiment 23 [C 627]).—Ligation of the ureter and the collateral blood supply, seventeen days' duration; small hydronephrosis; opposite kidney normal.

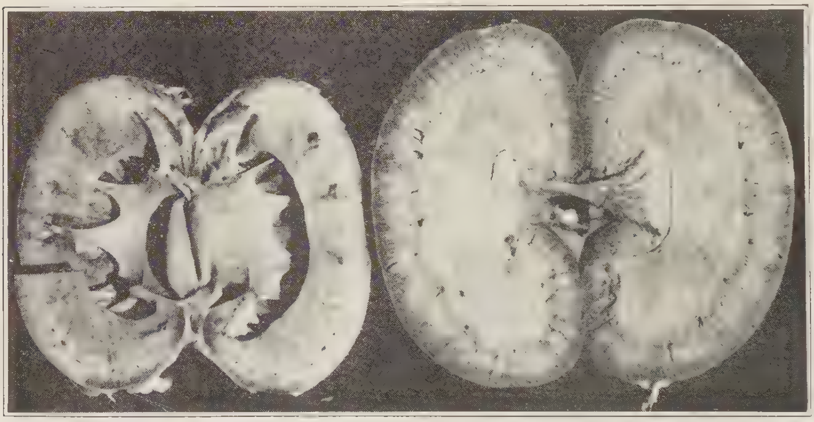

Fig. 28 (Series I, Group 2, Experiment 18 [B 608]).—Ligation of the ureter and the collateral blood supply, twenty-three days' duration; large hydronephrotic cavity with atrophy of the kidney; opposite kidney normal.

3. Pyonephrosis is more common if the collateral circulation has been ligated.

4. Progressive atrophic changes occur in the kidney in the same sequence as when the ureter alone is ligated.

5. Ligation of the ureter does not affect the general health of the

dog, since ten animals lived more than 100 days and two more than 400 days before being sacrificed.

In summarizing the observations made in Group 1 and in Group 2 of Series I, it is important to note that after the outflow of urine is obstructed by ligating the ureter the normal secretion of urine continues until the ureter and pelvis of the kidney are completely filled; after that, urinary secretion takes place under the abnormal condition of

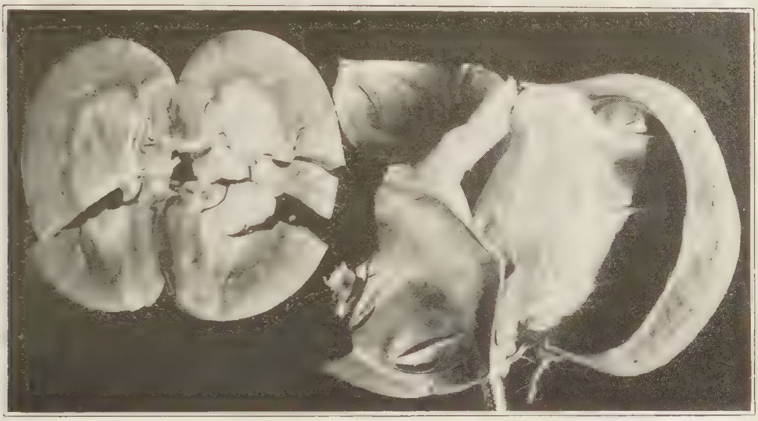

Fig. 29 (Series I, Group 2, Experiment 17 [B 722]).—Ligation of the ureter and the collateral blood supply, twenty-four days' duration; large hydronephrotic sac; atrophy of the kidney, particularly in the lateral portions; opposite kidney normal.

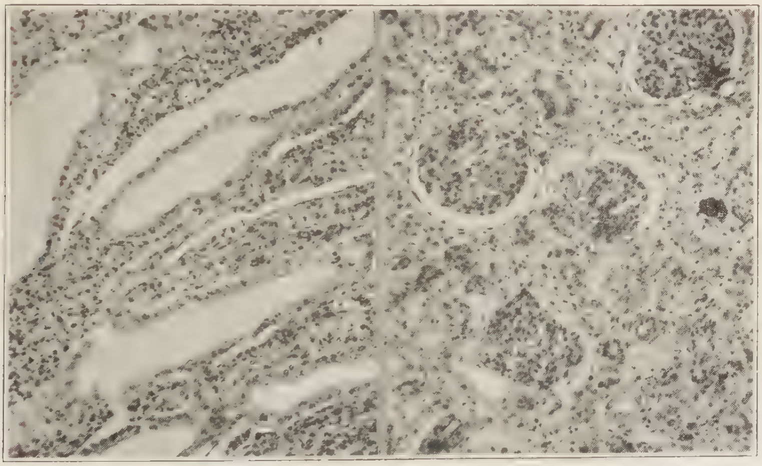

Fig. 30 (Series I, Group 2, Experiment 17 [B 722]).—Degeneration of the convoluted tubules; dilatation of the collecting tubules and glomeruli of kidney shown in Figure 29.

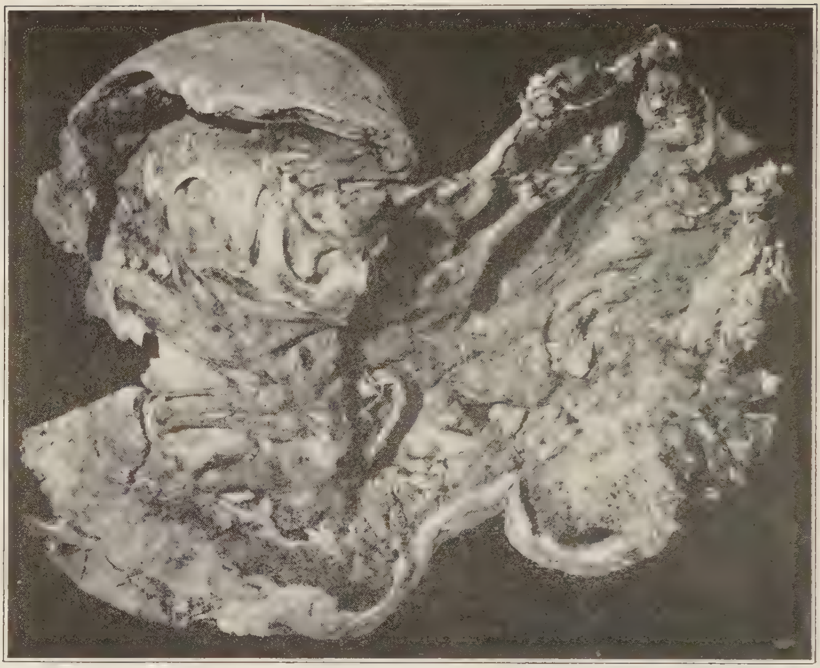

FIG. 31 (Series I, Group 2, Experiment 15 [C 92]).—Ligation of the ureter and the collateral blood supply, thirty-two days' duration; large pyonephrosis which ruptured, causing peritonitis and death.

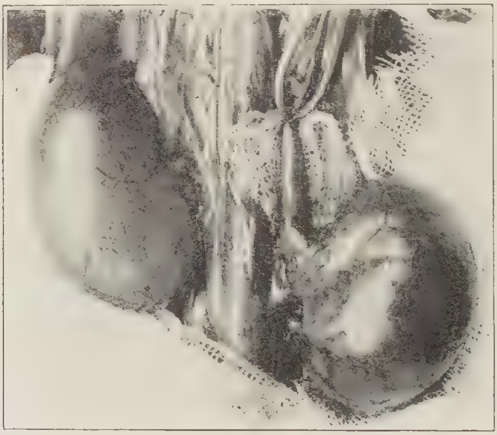

FIG. 32 (Series I, Group 2, Experiment 13 [B 990]).—Ligation of the ureter and the collateral blood supply, thirty-five days' duration; no dilatation of capsular vessels; large hydronephrotic cavity with atrophy of the kidney; with hydronephrotic sac smaller then opposite normal kidney.

back-pressure from the damming up of urine in the pelvis of the kidney, which immediately dilates because its walls are elastic and not capable of resisting this increased intrapelvic pressure. The secreting power of the kidney is greatest at the time of ligation of the ureter, gradually diminishing in direct proportion to the duration of the obstruction, as the increased intrapelvic pressure causes a compression of the renal

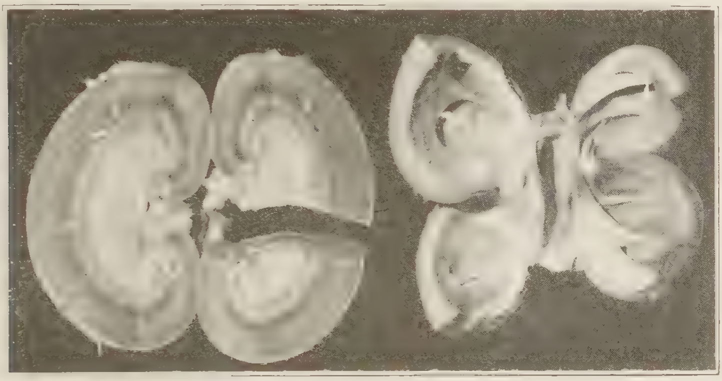

Fig. 33 (Series I, Group 2, Experiment 13 [B 990]).—Ligation of the ureter and the collateral blood supply, thirty-five days' duration; no dilatation of capsular vessels; large hydronephrotic cavity with atrophy of the kidney; kidney with hydronephrotic sac smaller than opposite normal kidney.

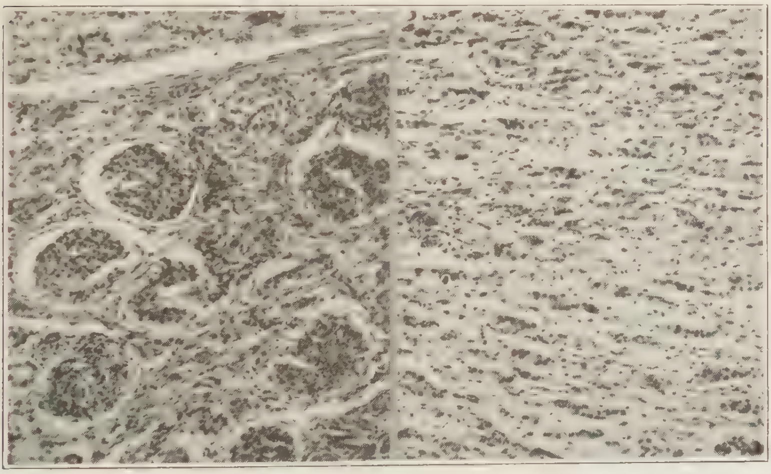

Fig. 34 (Series I, Group 2, Experiment 13 [B 990]).—Marked degeneration of tubules of cortex and medulla of kidney shown in Figures 32 and 33; glomeruli fairly well preserved in cortical portion proximal to the capsule.

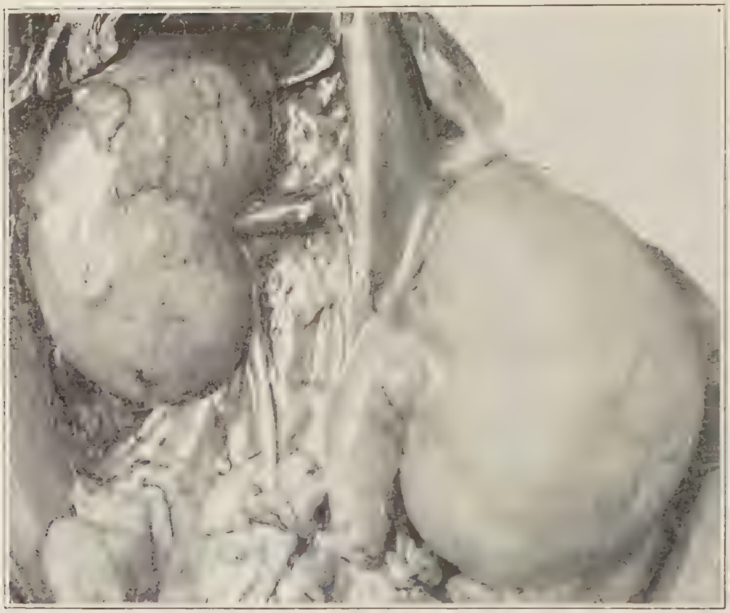

FIG. 35 (Series I, Group 2, Experiment 9 [B 721]).—Ligation of the ureter and the collateral blood supply, 149 days' duration; no dilatation of the capsular veins; large hydronephrotic kidney with dilated tortuous ureter; hydronephrotic kidney lower than opposite normal kidney.

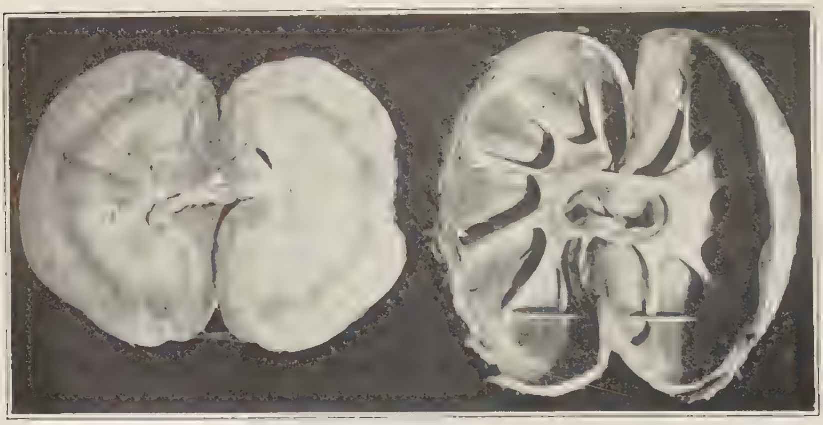

FIG. 36 (Series I, Group 2, Experiment 8 [B 997]).—Ligation of the ureter and the collateral blood supply, 150 days' duration; large hydronephrotic sac; complete destruction of renal parenchyma with persistence of connective tissue bands between the lobules; opposite kidney normal.

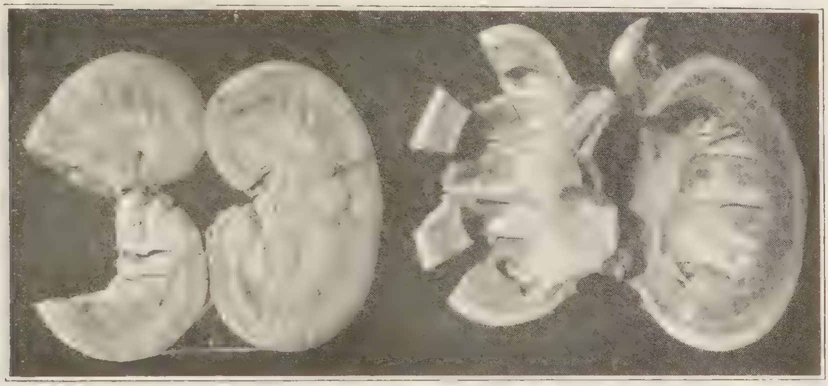

Fig. 37 (Series I, Group 2, Experiment 2 [C 730]).—Ligation of the ureter and the collateral blood supply, 422 days' duration; large hydronephrotic sac with almost complete destruction of the renal parenchyma except in the median sagittal portion; opposite kidney normal.

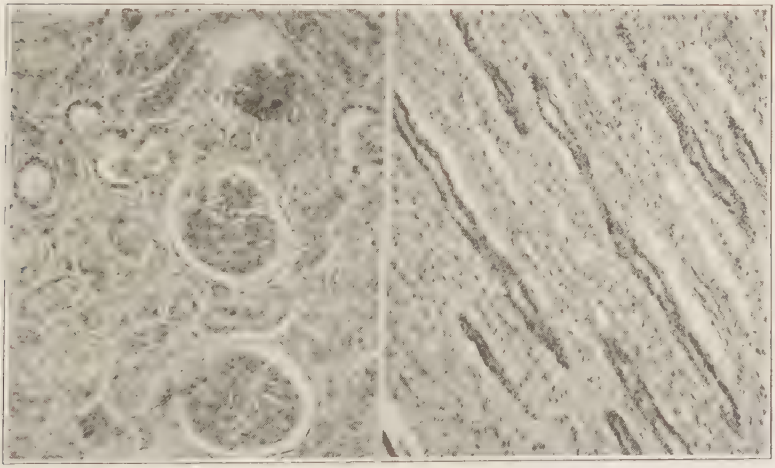

Fig. 38 (Series I, Group 2, Experiment 2 [C 730]).—Ligation of the ureter and the collateral blood supply, 422 days' duration; marked degeneration of the renal parenchyma of kidney shown in Figure 37; glomeruli well preserved.

parenchyma by flattening of the pyramids and thinning of the medulla and cortex and a damming back of urine in the tubules. This exerts pressure directly on the cells lining the tubules and results in decreased nutrition and atrophy of the renal parenchyma. The increased intrapelvic and intrarenal pressures cause a compression of the small venous capillaries where only low pressure obtains, thus partially obstructing the venous return. This produces a congestion and edema of the kidney, but does not completely obstruct the venous return, and blood continues to pass from the kidney through the renal vein although the amount is greatly diminished, and the glomerulus is the last renal structure to be destroyed. The partial obstruction of the venous return affects the renal parenchyma and secretory power of the kidney in two ways: It decreases the amount of blood passing through the kidney and consequently the amount of secretion possible. Likewise the amount of nutrition carried to the cells of the parenchyma must be diminished. Partial obstruction of the venous return is relieved in two ways: first, by dilatation of the capsular veins, and second, by absorption from the medullary portion of the kidney, which is in inverse proportion to the destruction of the renal parenchyma. Dilatation of the capsular veins is caused by increased intrarenal pressure and is secondary to the production of hydronephrosis, since a hydronephrotic sac develops when the collateral circulation is ligated. The partial compensation of the venous return by the dilatation of the capsular vessels permits a greater secretory activity of the kidney because of the increased blood supply and nutrition and results in a larger and more rapidly developing hydronephrosis, which in turn causes more speedy destruction of the parenchyma than is found when the collaterals are ligated. The production of hydronephrosis is dependent on the amount of resistance afforded by the pelvis to the increased intrapelvic pressure incident to the secretory activity, which is variable, but greatest at the time of obstruction, and gradually diminishes so that in four weeks no secretion is demonstrable. It is possible that this may be the explanation of the difference in the results obtained in experimental investigations in animals and the clinical observations noted in man, that is, in man the collateral venous circulation is practically negligible, and the pelvis and capsule of the kidney are more resistant. It seems that if it were possible to enclose the pelvis of the kidney and the ureter in a plaster of Paris cast and completely obstruct the outflow of urine, the increased intrapelvic pressure would become so great that it would stop all secretory activity and result in atrophy of the kidney.

SERIES II. THE EFFECT OF OCCLUSION OF THE VARIOUS VASCULAR RADICALS OF THE KIDNEY

The study of the results of ligation of the various vascular radicals of the kidney was undertaken with the view of determining the ultimate effect on the renal parenchyma and whether or not a collateral venous circulation would be established. It was shown by Bowman, in 1842, that the arterial radicals of the kidney were end arteries, but Hyrtl in 1882, was first to point out that there was no anastomosis between the branches of the renal arteries. These facts are often lost sight of by surgeons in various surgical procedures upon the kidney, as mentioned by Brödel in 1901.

Series II comprises four groups. The experiments in Groups 1 and 2 pertain to the arterial blood supply, and those in Groups 3 and 4, to the venous supply. The operative procedures were essentially the same in the four groups except that different vessels were ligated.

Group 1. *Ligation of the renal artery* (*five experiments*).—In this study it was my purpose to determine (1) the results produced on the kidney, (2) whether or not a collateral blood supply would be established, and (3), whether or not the omentum when wrapped about a decapsulated kidney would furnish sufficient blood to continue the function of the kidney.

After the kidney was exposed the renal artery was carefully dissected from the perirenal fat and doubly ligated and sectioned. As shown in Table 3 the renal artery alone was ligated in three dogs; the

TABLE 3.—SERIES II. THE EFFECT OF OCCLUSION OF THE VARIOUS VASCULAR RADICALS OF THE KIDNEY

Group 1.—Ligation of renal artery (five experiments)

Experiment		Animal	Date of operation	Duration of experiment, days	Renal artery ligated	Decapsulation of kidney and wrapping in omentum	Necropsy	Kidney tissue pale and degenerating	Collateral arterial circulation	Atrophy of kidney operated on	Weight of kidney operated on, gm.	Adhesions around kidney operated on	Weight of kidney not operated on, gm.
1	(190)	B828	3– 5–17	31	Left	..	214	+	0	+	10	....	40
2	(99)	B769	2–10–17	16	Left	+	90	+	0	+	18	Omentum	27
3	(53)	B742	1–27–17	10	Left	+	53	+	0	+	14	Omentum	26
4	(242)	B869	3–16–17	8	Left	..	173	+	0	+	30	....	45
5	(490)	C 47	7– 9–17	4	Right	..	419	+	0	+	38	....	42

artery was ligated and the kidney decapsulated and wrapped in omentum in two.

Sudden complete occlusion of the renal artery by ligation resulted in a gradual symmetric atrophy of the entire kidney. In Experiments 1, 4, and 5 collateral arterial anastomosis was not formed. In Experiments 2 and 3, of sixteen and ten days' duration, the kidney was wrapped in omentum, but this had no effect on the degree of atrophy of the kidney (Figs. 39, 40 and 41).

From these five experiments it is evident that (1) the renal artery is the only source of blood supply to the kidney, furnishing both nutritional and functional blood, and is a strict end artery; (2) a collateral arterial anastomosis is not formed after ligation of the renal artery; and (3) wrapping the kidney in omentum after decapsulation and ligation of the renal artery does not produce arterial anastomosis in order to supply the renal parenchyma and therefore has no effect on the development of atrophy.

Group 2. Ligation of one or more branches of the renal artery (sixteen experiments).—In man it is frequently necessary to ligate an aberrant vessel passing to the lower pole of the kidney, causing an intermittent obstruction to the outflow of urine and producing a hydronephrosis.

In sixteen animals after the kidney was exposed the branches of the renal artery were carefully dissected free from perirenal fat and one or more doubly ligated and sectioned (three to 526 days' duration) with the view of determining as accurately as possible what may be expected in man if for any reason the same procedure is necessary. In the dog there are usually four branches of the renal artery, two to the anterior surface and two to the posterior surface. The anterior vessels are the larger; they supply the anterior two-thirds of the kidney; the smaller posterior branches supply approximately the posterior third. They usually divide just inside the hilum into two smaller branches, one to each pole. For convenience of description these vessels have been termed anterior-superior and inferior, and posterior-superior and inferior, the areas of the kidney to which they pass being designated quadrants according to the vessel. This division on the basis of the distribution of the arterial branches is not accurate since the posterior branches supply less kidney tissue than the anterior vessels, and there is also a variation in the size of the superior and inferior branches, the size of the vessel being in accordance with the area supplied.

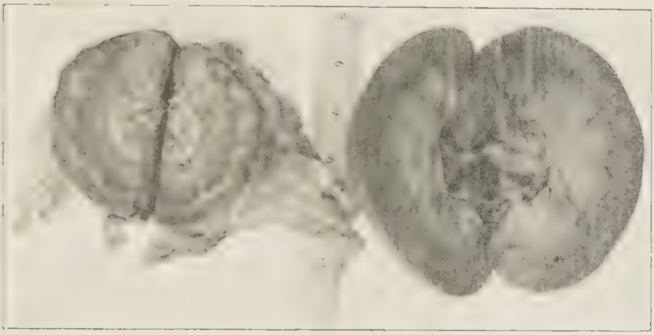

Fig. 39 (Series II, Group 1, Experiment 2 [B 769]).—Ligation of the left rena artery, kidney wrapped in omentum, sixteen days' duration; atrophy of the entire kidney which weighed 10 gm. Wrapping kidney in omentum did not affect the result

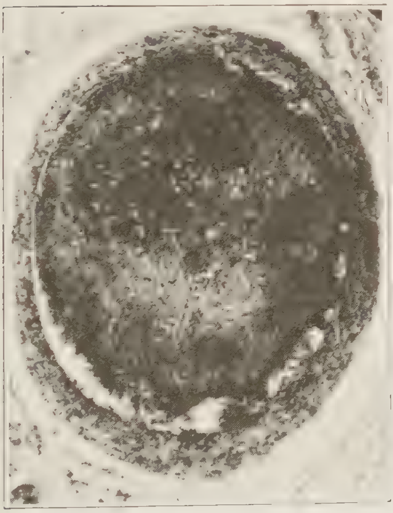

Fig. 40 (Series II, Group 1, Experiment 2 [B 769]).—Section of kidney shown in Figure 39; thrombosis of kidney vessels.

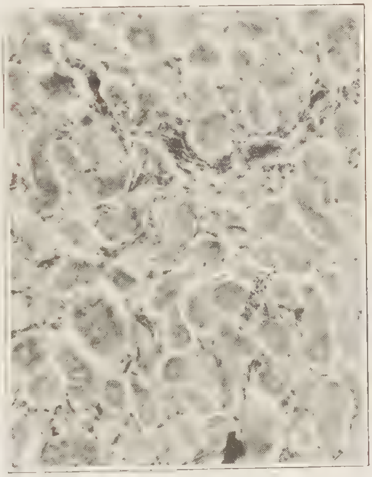

Fig. 41 (Series II, Group 1, Experiment 2 [B 769]).—Section of kidney shown in Figure 39; amblyoid degeneration of the renal parenchyma of the cortex and medulla.

Immediately following ligation of a branch of the renal artery there was marked congestion of the portion of kidney supplied by that vessel, and a bluish discoloration of the cortex with a sharp line of demarcation was produced. A linen thread was sutured accurately around the margin of this area so that it would be possible to determine whether or not the circulation in any part of the area was later restored and what the ultimate fate of this portion of the renal parenchyma was (Table 4 and Figs. 42 to 48).

TABLE 4.—SERIES II. THE EFFECT OF OCCLUSION OF THE VARIOUS VASCULAR RADICALS OF THE KIDNEY

Group 2.—Ligation of one or more branches of the renal artery (sixteen experiments).

	Experiment	Animal	Day of operation	Renal artery ligated	Branches of renal artery ligated				Duration of experiment, days	Atrophy of kidney					
					Anterior superior	Anterior inferior	Posterior superior	Posterior inferior		Decapsulation of kidney and wrapping in omentum	Necropsy	Anterior superior quadrant	Anterior inferior quadrant	Posterior superior quadrant	Posterior inferior quadrant
1	(273)	C444	4–29–18	Right	+	..	..	+	526	+	464	+	..	..	+
2	(442)	C569	7– 1–18	Right	..	..	..	+	464	..	465	..	..	..	+
3	(398)	C529	6–17–18	Right	..	..	+	+	...	..	...	..	..	+	+
				Left	+	..	+	..	348	+	261	+	..	+	
4	(265)	C438	4–22–18	Right	..	..	+	+	325	+	93	..	..	+	+
5	(331)	C477	5–20–18	Right	..	+	+	+	43	..	326	..	+	+	+
6	(364)	C505	6– 3–18	Right	+	..	+	..	...	..	...	..	..	+	
				Left	..	+	+	+	38	+	347	..	+	+	+
7	(274)	C445	4–29–18	Right	+	+	..	+	..	..	...	+	+	+	+
				Left	..	..	+	..	23	..	261	..	..	+	
8	(235)	C412	4– 4–18	Right	..	..	+	+	15	+	220	..	..	+	+
9	(291)	C456	5– 6–18	Right	+	+	..	..	...	..	...	+	+		
				Left	+	+	..	..	14	..	258	+	+		
10	(236)	C413	4– 8–18	Right	..	..	..	+	11	..	218	..	..	..	+
11	(257)	C430	4–15–18	Right	+	+	..	..	10	..	230	+	+		
12	(329)	C476	5–20–18	Left	+	+	..	..	7	..	271	+	+		
13	(256)	C429	4–15–18	Right	..	..	+	+	4	..	219	..	..	+	+
14	(225)	C402	4– 4–18	Right	+	+	..	..	4	..	180	+	+		
15	(224)	C401	4– 4–18	Right	..	..	+	+	4	..	179	..	..	+	+
16	(363)	C504	6– 3–18	Right	..	..	+	+	..	..	...	..	..	+	+
				Left	..	..	+	..	3	..	283	..	..	+	

These experiments show quite conclusively that (1) ligation of any branch of the renal artery causes atrophy of the area of renal parenchyma supplied by it; (2) each branch entering the kidney carries functional and nutritional blood to its respective area; and (3) there is no anastomosis between any of the branches of the renal artery.

Group 3. Ligation of the renal vein (eight experiments).—This phase of the problem was studied in order to determine (1) the results

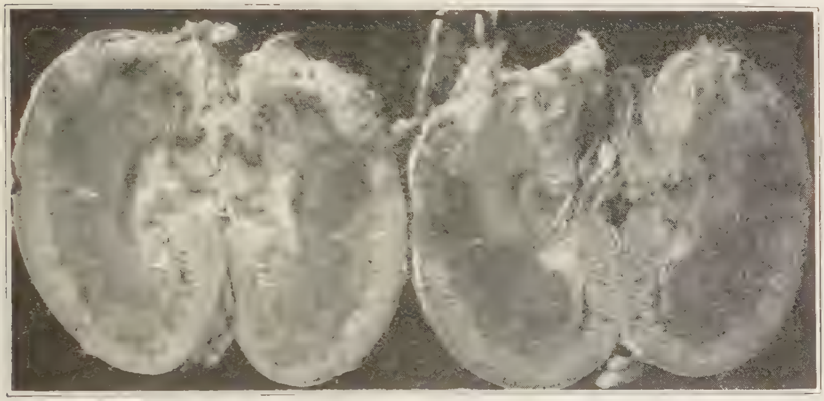

Fig. 42 (Series II, Group 2, Experiment 16 [C 504]).—Ligation of the posterior superior branch of left renal artery and of the posterior superior and inferior branches of the right artery, three days' duration; degeneration of the posterior poles and areas supplied by these branches.

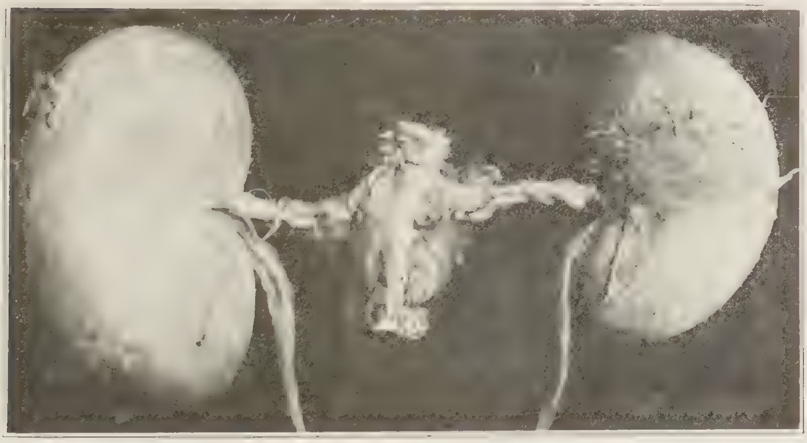

Fig. 43 (Series II, Group 2, Experiment 11 [C 430]).—Ligation of the anterior, superior and inferior branches of the right renal artery, ten days' duration; atrophy of the anterior pole of the right kidney; left kidney normal.

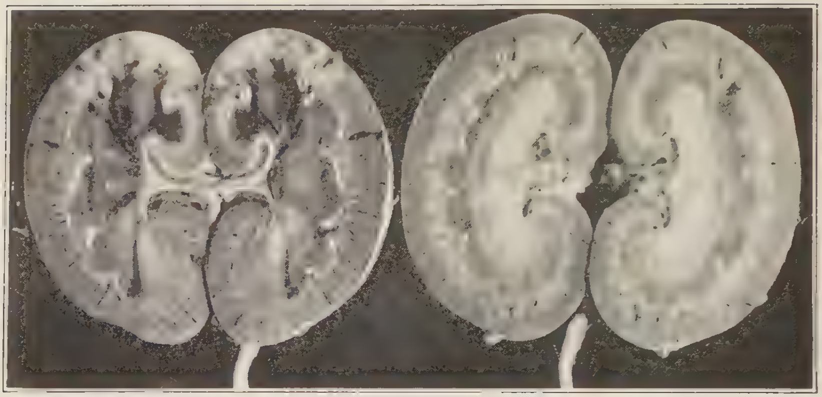

Fig. 44 (Series II, Group 2, Experiment 11 [C 430]).—Ligation of the anterior superior and inferior branches of the right renal artery, ten days' duration; atrophy of the anterior pole of the right kidney; left kidney normal.

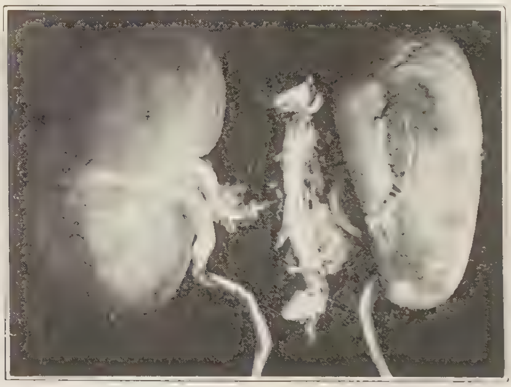

Fig. 45 (Series II, Group 2, Experiment 10 [C 413]).—Ligation of the posterior inferior branch of the right renal artery, eleven days' duration; atrophy of the renal tissue supplied by this branch; left kidney normal.

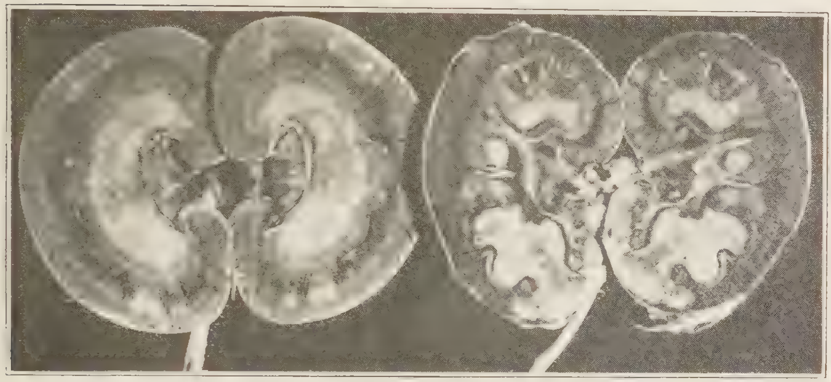

Fig. 46 (Series II, Group 2, Experiment 8 [C 412]).—Ligation of the posterior and inferior branches of the right renal artery; right kidney decapsulated and wrapped in omentum, fifteen days' duration; atrophy of the lower pole of the right kidney supplied by the posterior branch; results not affected by decapsulation and wrapping in omentum; new capsule formed in right kidney.

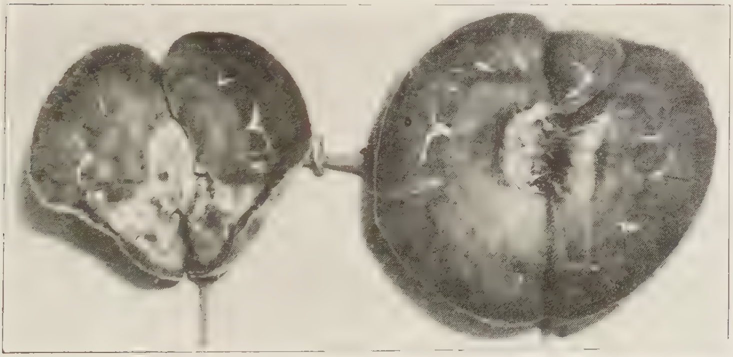

Fig. 47 (Series II, Group 2, Experiment 6 [C 505]).—Ligation of the anterior superior and posterior superior branches of the right renal artery and of the anterior inferior and posterior inferior branches of the left renal artery; both kidneys decapsulated and wrapped in omentum, thirty-eight days' duration; atrophy of area supplied by these vessels; no effects from wrapping kidney in omentum; new capsule formed in both kidneys.

produced on the kidney, (2) whether or not a collateral venous circulation would be established and if so of what veins it would be comprised, and (3) whether or not this collateral venous circulation would be capable of assuming the function of the renal vein and of maintaining a functionating kidney.

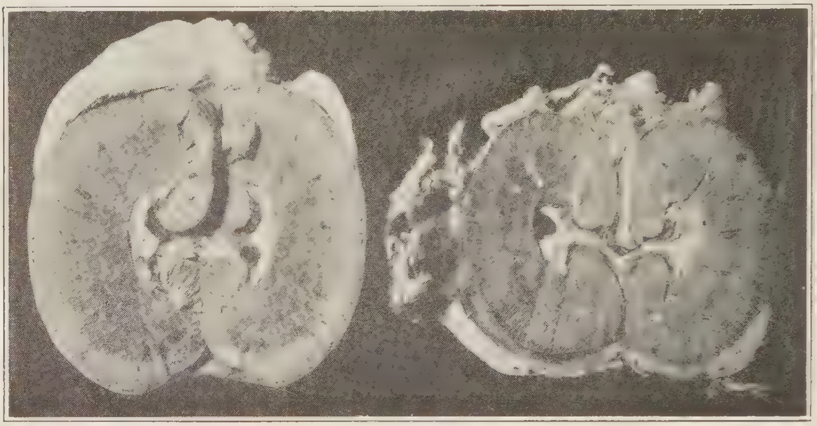

Fig. 48 (Series II, Group 2, Experiment 4 [C 436]).—Ligation of the posterior superior and inferior branches of the right renal artery; right kidney decapsulated and wrapped in omentum, 325 days' duration; atrophy of the posterior half of the right kidney; no effects from decapsulation and wrapping kidney in omentum.

Lindemann, in 1898, stated that after the renal vein is obstructed a collateral circulation is developed sufficient to maintain the function of the kidney. Testut, in 1917, stated that the collateral circulation is capable of maintaining the renal function in part. Tuffier and Lejars stated that obliteration of the renal vein results in the formation of a collateral circulation whereby venous blood from the kidney is carried back to the general circulation through this plexus by four routes, (1) suprarenal and inferior diaphragmatic, (2) ureteric and spermatic or ovarian, (3) subcutaneous plexuses of the lumbar veins, and (4) a plexus which surrounds the last intercostal, ileo-inguinal, and ileo hypogastric nerves.

After the kidney was exposed the renal vein was carefully dissected from the perirenal fat at the hilum and doubly ligated and sectioned (Table 5).

Immediately after the renal vein was ligated there was a marked enlargement and bluish discoloration of the kidney from venous congestion. The organ became very tense from the engorgement of blood. This was followed almost immediately by dilatation of the capsular vessels, especially the suprarenal, the ovarian or spermatic, and branches to the lumbar veins. In a few instances a vein was found passing directly from the capsule of the kidney to the renal vein. In most instances two or more of these dilated capsular vessels were found.

TABLE 5.—SERIES II. THE EFFECT OF OCCLUSION OF THE VASCULAR RADICALS OF THE KIDNEY

Group 3.—Ligation of the renal vein (eight experiments).

							Dilatation							
	Experiment	Animal	Date of operation	Duration of experiment, days	Ligation of renal vein	Necropsy	Capsular veins	Suprarenal veins	Ovarian or spermatic veins	Lumbar veins	Congestion of kidney operated on	Atrophy of kidney operated on	Weight of kidney operated on, gm.	Weight of kidney not operated on, gm.
1	(156)	B804	2–26–17	345	Left	49	+	+	+	+	..	+	5	30
2	(291)	B902	3–26–17	132	Right	453	+	+	+	..	..	+	4	20
3	(50)	B739	1–27–17	12	Left	55	+	..	+	+	+	+	24	30
4	(418)	C548	6–24–18	10	Left	336	+	+	+	..	+	+	25	37
5	(126)	B795	2–19–17	6	Left	87	+	+	+	+	+	..	34	30
6	(246)	B871	3 17–17	4	Left	164	(Kidney ruptured in several places; hemorrhage cause of death)						200	57
7	(240)	B868	3–16–17	4	Left	152	+	+	+	..	+	..	30	20
8	(304)	B913	3–28–17	2	Left	190	+	+	+	..	+	..	32	25

In Experiments 5, 6, 7, and 8, of six, four, and two days' duration respectively, there was marked congestion and enlargement of the kidney with beginning degenerative changes (Figs. 49, 50, and 51).

In Experiment 6 the dog died on the fourth day. At necropsy it was found that death was caused by hemorrhage from the kidney operated on, which had ruptured in several places (Figs. 36 and 37) allowing the blood to escape and infiltrate the surrounding tissues. This kidney weighed 200 gm. and showed enormous congestion throughout the parenchyma.

In Experiments 3 and 4, of twelve and ten days' duration respectively, there was beginning atrophy of the entire kidney. In both there was pronounced dilatation of the capsular veins.

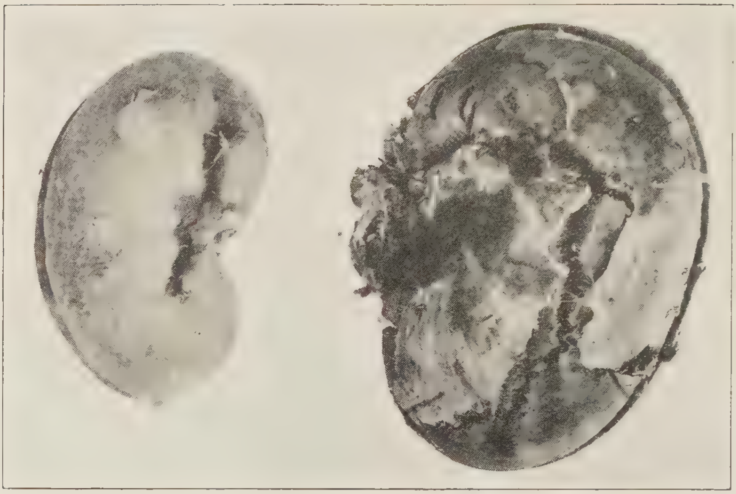

Fig. 49 (Series II, Group 3, Experiment 6 [B 871]).—Ligation of the left renal vein, four days' duration; rupture of the left kidney from engorgement of blood, causing death from hemorrhage; right kidney normal.

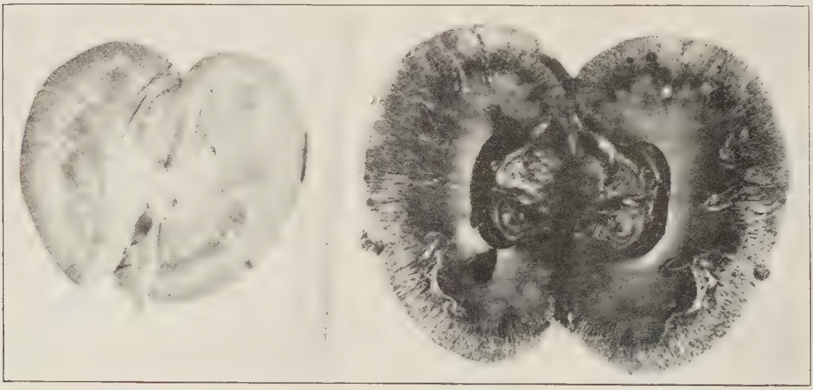

Fig. 50 (Series II, Group 3, Experiment 6 [B 871]).—Ligation of the left renal vein, four days' duration; rupture of the left kidney from engorgement of blood, causing death from hemorrhage; right kidney normal.

In Experiments 1 and 2, of 132 and 345 days' duration respectively, there was a marked atrophy of the entire kidney. In Experiment 1, only a small nodule of kidney tissue was left. In Experiment 2, the remaining kidney tissue was symmetrically atrophied and weighed 4 gm. at the end of 345 days (Fig. 52).

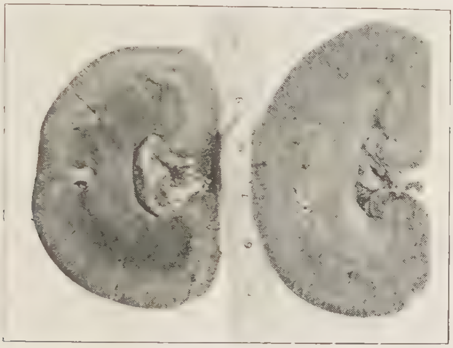

Fig. 51 (Series II, Group 3, Experiment 5[B 795]).—Ligation of the left renal vein, six days' duration; marked congestion of left kidney, weight 34 gm.; right kidney normal, weight 36 gm.

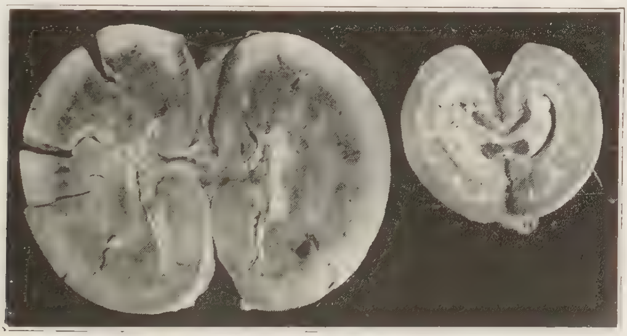

Fig. 52 (Series II, Group 3, Experiment 5 [B 795]).—Ligation of the right renal vein, 132 days' duration; atrophy of entire kidney, weight 4 gm.; left kidney normal, weight 20 gm.

This group of experiments shows that (1), there is a symmetrical atrophy of the kidney after complete sudden occlusion of the renal veins; (2) a partial venous collateral circulation to the kidney is established comprising chiefly the ovarian or spermatic veins, the suprarenal veins, and branches of the lumbar veins; (3) the collateral circulation of the kidney is not capable of assuming the function of the renal vein and maintaining a functionating kidney; and (4) ligation of the renal vein in a dog may cause the kidney to rupture.

Group 4. Ligation of one of the larger branches of the renal vein (two experiments).—This work was undertaken with the view of determining whether or not the capsular vessels would be dilated after partial obstruction of the venous return from the kidney, and whether or not the venous radicals of the kidney would anastomose.

The surgical procedure was the same as that used in former groups except that after the kidney was exposed the larger of the two main branches of the renal vein was dissected free from the perirenal fat and doubly ligated and sectioned. Two experiments were made (Table 6).

TABLE 6.—SERIES II. THE EFFECTS OF OCCLUSION OF THE VARIOUS VASCULAR RADICALS OF THE KIDNEY

Group 4.—Ligation of one of the larger branches of the renal vein.

	Experiment	Animal	Date of operation	Duration of experiment, days	Ligation of renal vein	Ligation of one branch of renal vein	Necropsy	Congestion of kidney operated on	Atrophy of kidney operated on	Weight of kidney operated on, gm.	Weight of kidney not operated on, gm.
1	(416)	C546	6–24–18	359	Right	Posterior anterior	283	0	0	32 Right	34 Left
2	(393)	C524	6–10–18	37	Left	Posterior	572	0	0	34	37

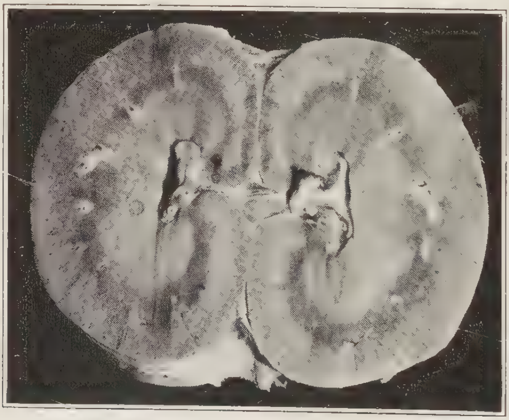

FIG. 53 (Series II, Group 4, Experiment 2 [C 524]).—Ligation of one branch of the right renal vein, thirty-seven days' duration; right kidney normal.

In Experiment 1, the dog was sacrificed after 359 days. At necropsy it was found that the kidney was normal in size and that no change had taken place in the renal parenchyma but the capsular vessels were slightly dilated.

In Experiment 2, the animal died on the thirty-seventh day. At necropsy the kidney was normal in size and there was no change in the renal parenchyma, but a moderate dilatation of the capsular vessels (Fig. 53).

SERIES III. THE EFFECT ON THE KIDNEY AND URETER OF TRAUMA TO THE URETER

The frequency with which the ureter is accidentally and unavoidably traumatized during the course of various surgical procedures is very hard to determine. It is known that the ureter is sometimes accidentally clamped with an artery forceps during operation in the vicinity.

Group 1. *Clamping of the ureter* (*eleven experiments*).—A review of the literature did not reveal any record of other studies of the effect on the kidney and ureter of clamping the ureter.

The operative procedure was essentially the same as that used in Series II. The ureter was exposed and crushed with a Kocher artery forceps for from one to thirty minutes and then replaced behind the peritoneum.

The eleven experiments of from four to 251 days' duration do not complete the investigation, but Table 7 indicates the results obtained to date (Figs. 54, 55 and 56).

Experiment 1 demonstrates the end-results on the kidney. The right ureter was crushed with a Kocher clamp to the third notch for ten minutes. The animal was sacrificed in 251 days. The ureter was almost completely constricted but water could be forced through the constricted area with a piston syringe. Both the ureter and pelvis were moderately dilated above the point of constriction. The kidney was small with a large hydronephrotic cavity (Fig. 56), the parenchyma being almost entirely destroyed by pressure atrophy; the entire organ weighed 18 gm. The capsular veins were not dilated, but there was compensatory hypertrophy of the opposite kidney which weighed 50 gm. The condition was very similar to that found in Group 2, Series I, in which the ureter and the collateral veins were doubly ligated and sectioned.

TABLE 7.—SERIES III. THE EFFECT ON THE KIDNEY AND URETER OF TRAUMA TO THE URETER

Group 1.—Clamping the ureter (eleven experiments).

	Experiment	Animal	Date of operation	Duration of experiment, days	Ureter clamped	Minutes ureter clamped	Notch of Kocher clamp	Necropsy	Condition of clamped ureter			Appearance of kidney with clamped ureter	Hydronephrosis	Dilatation of capsular veins
									Area of degeneration	Partial constriction	Dilatation			
1	(349)	B953	4–16–17	251	Right	10	Third	619	.....	+	+	Normal	Marked (weight 18 gm.)	0
2	(262)	B883	3–19–17	36	Right	30	Fourth	278	.....	+	Seven to eight times	Normal (weight 34 gm.)	Light Small	0
3	(348)	B952	4–16–17	23	Right	30	Third	318	.....	Slight	Slight	Normal	....	0
4	(191)	B829	3– 5–17	20	Right	5	Second	194	.....	+	0	Normal	....	0
5	(192)	B830	3– 5–17	10	Right	10	Second	144	+	+	0	Normal	....	0
6	(260)	B881	3–19–17	7	Right two times	3	Second	181	+	+	0	Normal	....	0
7.	(225)	B799	3–13–17	6	Left four times	1	Second	148	Slight	.....	0	Normal	....	0
8	(664)	B746	9– 9–18	5	Left	45	Second	523	+	+	+	Normal	....	0
9	(333)	B937	4– 7–17	5	Right	30	Third	253	+	+	Two times	Normal	....	0
10	(318)	B923	4– 2–17	4	Right	30	Fourth	215	.....	+	Four times	Normal	Small	0
11	(379)	B974	4–30–17	4	Left	30	Third	417	+	.....	Slight	Normal	....	0

In Experiment 2, the right ureter was clamped with a Kocher forceps to the fourth notch for thirty minutes. The dog died in thirty-six days. At necropsy a partial constriction of the ureter was found at the point of application of the clamp. The ureter was dilated seven to eight times its normal size above the point of constriction, and three times normal below it. There was a moderate degree of dilatation of the pelvis, a small hydronephrotic cavity, and slight

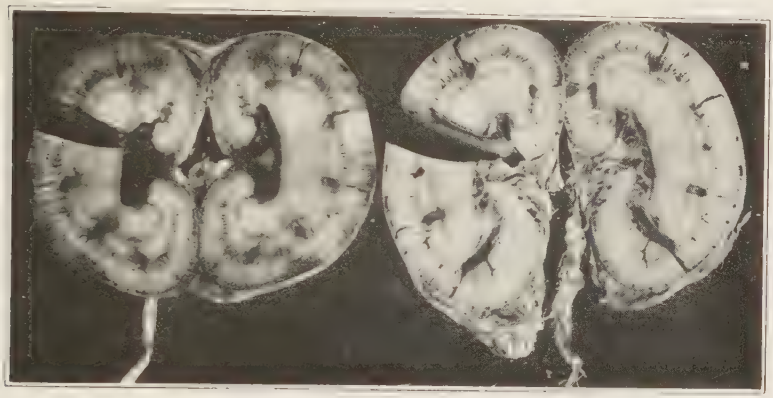

Fig. 54 (Series III, Group 1, Experiment 10 [B 923]).—Clamping of the right ureter, thirty minutes; necropsy after four days; slight constriction of the right ureter which was dilated to four times its normal size; slight hydronephrosis of the right kidney; left kidney normal.

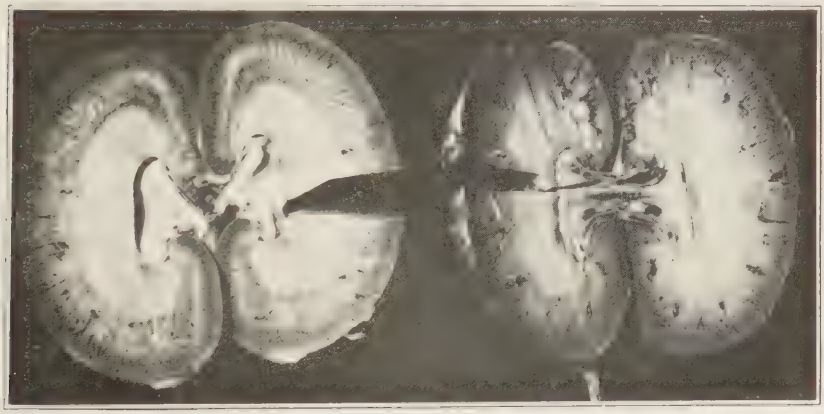

Fig. 55 (Series III, Group 1, Experiment 2 [B 883]).—Clamping of the right ureter, thirty minutes; necropsy after thirty-six days; partial constriction of the right ureter which was dilated to seven or eight times its normal size; slight hydronephrosis of right kidney.

atrophy of the renal parenchyma. The kidney weighed 30 gm. The capsular veins were not dilated. The opposite kidney weighed 37 gm. (Fig. 55).

In Experiments 3 to 11 inclusive, of from four to twenty-three days' duration, there was a degenerating area at the point of application of the clamp which gradually formed into scar tissue, depending on the duration of the experiment. This scar tissue produced a stricture of the ureter with varying degrees of dilatation of the ureter above it (Fig. 54).

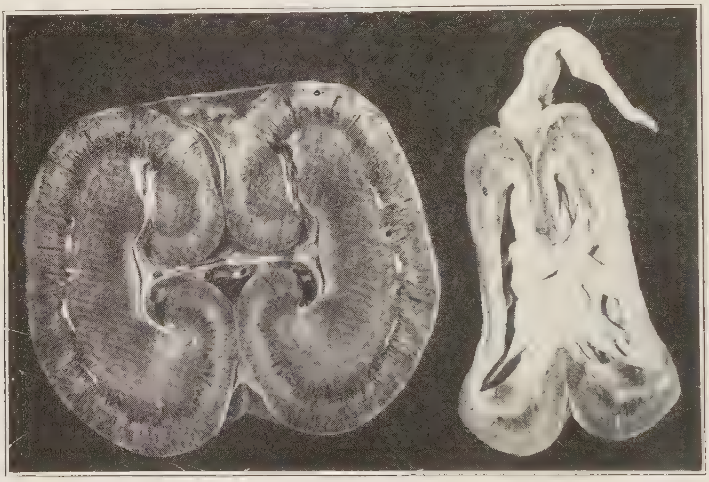

Fig. 56 (Series III, Group 1, Experiment 1 [B 953]).—Clamping of right ureter for ten minutes; necropsy after 251 days; partial constriction with dilatation of the right ureter; large hydronephrotic sac with atrophy of the right kidney; left kidney normal.

The study of this group of experiments shows that (1) injury to the ureter by crushing with an arterial forceps causes degenerative changes at the point of application, resulting in the formation of scar tissue which produces a partial constriction that may later progress to complete stricture; (2) there is dilatation of the ureter and pelvis in most instances which may progress to the point of hydronephrosis and degeneration of the kidney, with no dilatation of the capsular veins; and (3) no leakage of urine follows the application of a clamp to the ureter.

Group 2. Stripping of the ureter.—In various surgical procedures on the kidney, ureter, and bladder, and in operations on other organs in their vicinity, it is often necessary to strip the ureter for a distance from the surrounding tissue. The practical significance of the extent to which this may be done is of the utmost importance to the surgeon because of its bearing on the end-results of various surgical procedures. Stewart and Barber, in a series of nine experiments on dogs produced ureteral paralysis by stripping the ureter of all nerve, vessel, and lymphatic connections from the pelvis of the kidney to the bladder. This ureteral paralysis was accompanied by urinary stasis and distention of the kidney in 66 per cent of the cases.

Six experiments ranging from fourteen to seventy-four days in duration were made in this group. The operative procedure is essentially the same in each instance. After the ureter was exposed it was lifted from its bed and stripped with a piece of gauze for a distance of from 2 inches to its entire length and dropped back into the abdominal cavity with care to preserve as much of the blood supply as possible.

A study of the results obtained indicate that the ureter may be stripped of its surrounding tissues without permanent injury or deleterious effect on the kidney, providing its blood supply is preserved, since pathologic change was not found in the kidney or ureter in a single instance (Table 8).

TABLE 8.—SERIES III. THE EFFECT ON THE KIDNEY AND URETER OF TRAUMA TO THE URETER

Group 2.—Stripping the ureter (six experiments).

Experiment	Animal	Date of operation	Duration of experiment, days	Ureter stripped with gauze	Blood supply preserved	Distance of stripping	Necropsy	No change in ureter	Condition of kidney operated on
1 (583)	C107	8–20–17	74	Left	+	Entire length	317	+	Normal
2 (536)	C 75	7–30–17	41	Right	+	10 cm.	372	+	Normal
3 (285)	B899	3–24–17	31	Right	+	7.5 cm.	277	+	Normal
4 (191)	B829	3– 5–17	26	Left	+	5 cm.	194	+	Normal
5 (525)	C 72	7–27–17	22	Left	+	10 cm.	490	+	Normal
				Right	+	Entire length		+	Normal
6 (224)	B783	3–13–17	14	Left	+	Entire length	186	+	Normal

Group 3. Anastomosis of the ureters (twenty-two experiments).—Ureters are sometimes cut during the course of various surgical procedures in their vicinity, and not infrequently the ureter is severed by accident, fractures, and so forth. In order to determine the best method of anastomosing these injured ureters twenty-two experiments were made. The operative procedure was the same as previously described, up to the point of exposing the ureter. The ureter was completely cut across in each instance.

In five experiments (Method A) the cut ends of the ureter were anastomosed, end-to-end, with interrupted silk sutures. In thirteen experiments (Method B) the anastomosis was made by drawing the proximal end into the distal end for a distance of 0.625 cm., using three interrupted silk sutures, one at the lower end of the anastomosis and two at the upper end. In the remaining four experiments (Method C) the proximal end of the ureter was anastomosed into the side of the opposite ureter and sutured behind the peritoneum (Table 9).

Method A: End-to-end anastomosis.—Three of the five animals in this group (Experiments 1, 2, and 3), died the third day from peritonitis from urinary leakage. In Experiment 4, the animal died the nineteenth day from sepsis, resulting from an abscess which had formed at the site of the anatomosis and had burrowed into the pelvis, forming a large pocket of pus. In Experiment 5, the animal was sacrificed the fifty-sixth day. At necropsy a slight constriction and dilatation and a slight hydronephrosis were found (Fig. 57).

Method B: Cuff anastomosis.—This group consists of thirteen experiments of from five to 223 days' duration. In Experiment 6, the animal died the fifth day from peritonitis from urinary leakage, the only case of urinary leakage in this group. In Experiments 7 and 10, the ureters were markedly narrowed at the point of anastomosis, causing a partial constriction and dilatation of the ureter above this point with atrophy of the kidney and a moderate degree of hydronephrosis. In the remaining ten experiments the ureter was slightly constricted at the point of anastomosis, in most cases producing a slight dilatation of the ureter. Little or no effect was produced on the kidney in five cases, and a slight hydronephrosis in five cases (Figs. 56, 59 and 60) .

Method C: Uretero-ureterostomy.—In Experiments 19, 20, and 21 the animals died the second, third, and fourth days respectively, after

Table 9.—Series III. The Effect on the Kidney and Ureter of Trauma to The Ureter

Group 3.—Anastomosis of ureters (twenty-two experiments).

	Experiment	Animal	Date of operation	Duration of experiment, days	End-to-end anastomosis	Cuff anastomosis	Uretero-ureterostomy	Necropsy	Slight constriction at anastomosis	Marked obstruction at anastomosis	Dilatation of ureter above anastomosis	Urinary leakage	Condition of kidney operated on
A1	(313)	B920	3–31–17	3	Right	.....	.....	199	..	...	.....	+	
A2	(443)	C 19	6–11–17	3	Right	.....	.....	371	..	..	.....	+	
A3	(483)	C 43	7– 6–17	3	Right	.....	.....	413	..	..	.....	+	
A4	(314)	B921	3–31–17	19	Right	.....	.....	233	..	..	.....	+	
A5	(334)	B938	4– 9–17	56	Right	.....	.....	344	..	..	Slight	0	Slightly hydronephrotic
B6	(452)	C 28	6–22–17	5	.....	Right	.....	397	..	..	......	+	
B7	(617)	C127	8–31–17	14	.....	Right	.....	522	+	+	.....	0	Atrophic
B8	(600)	C119	8–27–17	18	.....	Right	.....	520	+	..	Slight	0	Normal
B9	(469)	C 36	7– 2–17	36	.....	Right	.....	460	+	..	0	0	Normal
B10	(489)	C 46	7– 9–17	43	.....	Right	.....	493	+	+	+	0	Atrophic
B11	(454)	C 30	5–25–17	48	.....	Right	.....	469	0	..	Slight	0	Normal
B12	(589)	C112	8–24–17	49	.....	Right	.....	538	+	..	Slight	0	Slightly hydronephrotic
B13	(630)	C135	9–10–17	60	.....	Right	.....	597	0	..	Slight	0	Normal
B14	(336)	B940	4– 9–17	67	.....	Right	.....	373	+	..	Slight	0	Hydronephrotic
B15	(625)	C131	9– 7–17	81	.....	Right	.....	623	0	..	Slight	0	Normal
B16	(599)	C118	8–27–17	95	.....	Right	.....	633	+	..	Slight	0	Hydronephrotic
B17	(453)	C 29	6–22–17	187	.....	Right	.....	611	0	..	Slight	0	Normal
B18	(455)	C 31	6–25–17	223	.....	Right	.....	8	+	..	+	0	Hydronephrotic
C19	(470)	C 37	7– 2–17	2	...	.....	Right into left	402	....	....	....	+	
C20	(498)	C 55	7–13–17	3	.....	.....	Right into left	420	..	..	......	+	
C21	(499)	C 56	7–13–17	4	.....	.....	Right into left	423	..	..	.....	+	Left, hydronephrotic
C22	(491)	C 48	7– 9–17	25	.....	.....	Right into left	449	..	+ Left	.....	0 ..	Left, atrophic and slightly hydronephrotic

operation, from peritonitis from urinary leakage. In Experiment 22 the animal was sacrificed the twenty-fifth day. At necropsy it was found that the anastomosis had healed perfectly, apparently without urinary leakage. The anastomosed ureter was dilated from partial constriction at the point of implantation and its kidney slightly atrophied. The recipient ureter was slightly dilated above the point of anastomosis, but the kidney appeared to be normal (Fig. 61).

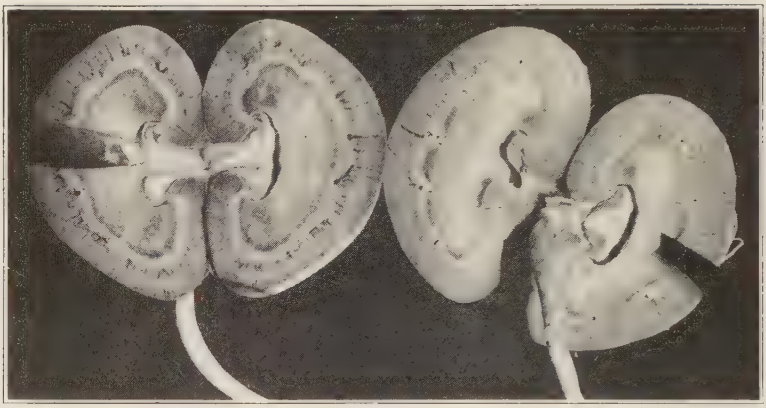

Fig. 57 (Series III, Group 3, Experiment 5 [B 936]).—End-to-end anastomosis of the right ureter; fifty-six days duration; slight constriction and dilatation of the right ureter, slight hydronephrosis of the right kidney; left kidney normal.

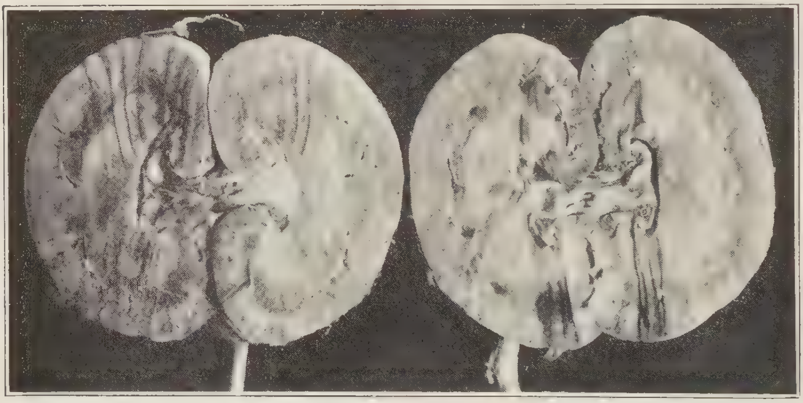

Fig. 58 (Series III, Group 3, Experiment 15 [C 131]).—Cuff anastomosis of the right ureter, eighty-one days' duration; slight dilatation of the right ureter; no stricture; right kidney normal; left kidney normal.

From these experiments it seems that in the dog cuff anastomosis is the method of choice as in one case only leakage of urine occurred, and that peritonitis resulting from urinary leakage is the most frequent cause of failure and death in anastomosing ureters.

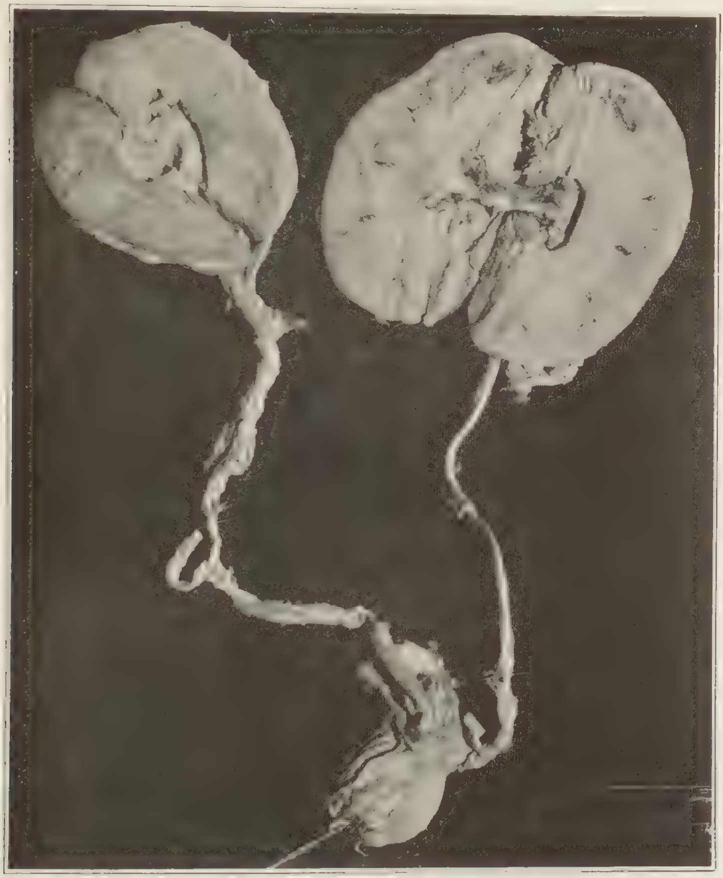

Fig. 59 (Series III, Group 3, Experiment 10 [C 46]).—Cuff anastomosis of the right ureter, forty-three days' duration; partial constriction and dilatation of the right ureter; slight hydronephrosis with atrophy of the right kidney; left kidney normal.

SERIES IV. THE EFFECT OF DECAPSULATION OF THE KIDNEY

Great variations have been obtained in the results by experimental decapsulation of the normal kidney, particularly the distribution of the blood vessels that are formed to repair the injury. The capsule is rapidly formed with an increase in the connective tissue of the cortex.

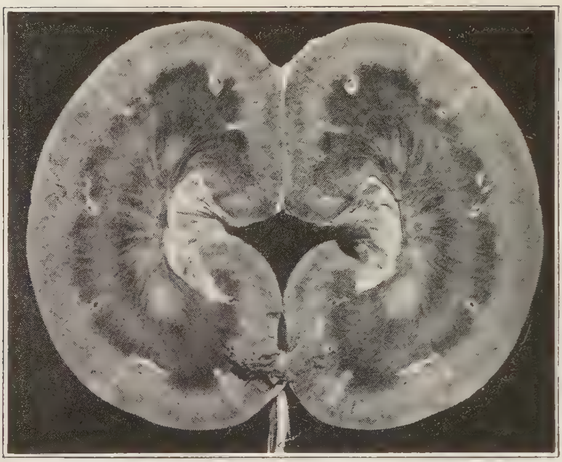

Fig. 60 (Series III, Group 3, Experiment 8 [C 119]).—Cuff anastomosis of the right ureter, eighteen days' duration; slight constriction and dilatation of the right ureter; right kidney normal.

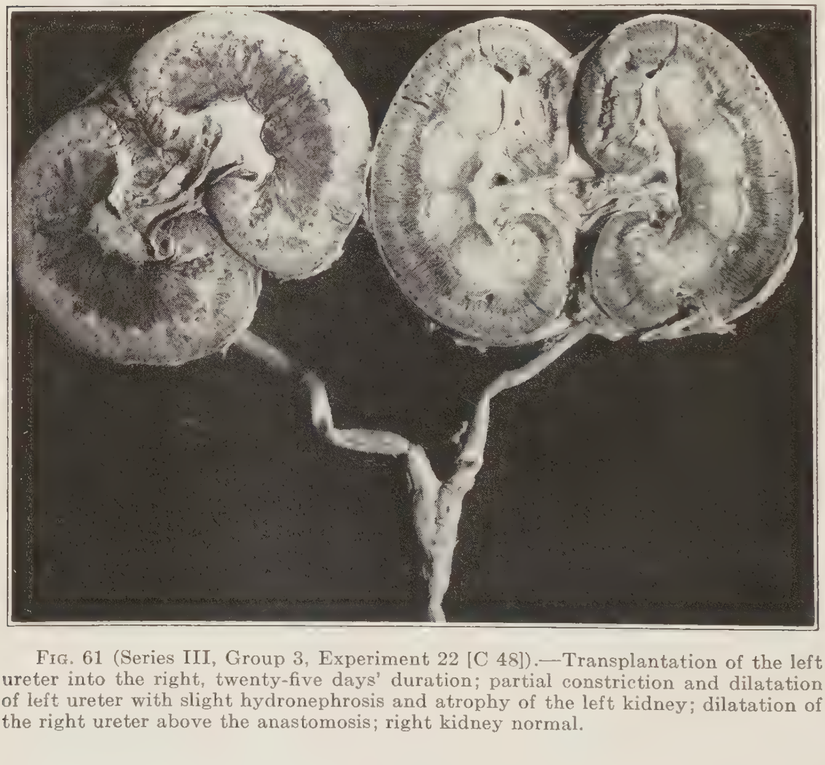

Fig. 61 (Series III, Group 3, Experiment 22 [C 48]).—Transplantation of the left ureter into the right, twenty-five days' duration; partial constriction and dilatation of left ureter with slight hydronephrosis and atrophy of the left kidney; dilatation of the right ureter above the anastomosis; right kidney normal.

There is still some controversy over the derivation of the new capsule and the distribution of the new blood supply. Emerson, in 1903, after twenty experiments on dogs, concluded that the kidney forms a new capsule with marked vascular connections with the surrounding viscera, but not with the fatty capsule of the kidney, and that bands of connective tissue penetrate the renal parenchyma, simulating a diffuse nephritis. Johnson, in 1903, from experiments on fifteen dogs, concluded that the kidney forms a new capsule and that there is round-cell infiltration of the cortex, but no anastomosis between the renal and peritoneal blood channels. Gifford, in 1904, from experiments on the normal kidney of rabbits, found that a new very vascular capsule is formed after decapsulation, but that these new vessels do not anastomose with the branches of the renal artery of the cortex. Hall and Herxheimer, working with rabbits, observed the formation of a new vascular fibrous capsule, but very few new blood channels between the kidney and the adherent tissues. Siter, in 1912, from two series of experiments on cats and dogs, in two stages, found that a new capsule forms from the omentum and that a collateral circulation is established in ten days which is capable of maintaining the kidney function properly when the renal vessels are tied off.

Group 1. *Decapsulation of the kidney and wrapping it in omentum* (*thirteen experiments*). -These experiments were undertaken for the purpose of determining (1) whether a new capsule would form; (2) whether the capsular circulation would be increased or decreased; (3) whether the branches of the renal artery and the arterial capsular blood vessels would anastomose, and (4) whether changes are produced in the renal parenchyma. Other points in relation to the decapsulation of diseased kidneys have not been completed.

The operative procedures were the same as those in the other series up to the point of exposing the kidney. In the majority of instances both layers of the fibrous capsule of the kidney were removed, with care to injure the renal parenchyma as little as possible. It is usually difficult to remove the inner, thin, reticular layer of the capsule because of intimate association with the connective tissue surrounding the tubules of the cortex. There was considerable oozing of blood from the surface of the kidney after its capsule was removed; this was controlled by compression with gauze for about four or five minutes. The decapsulated kidney was then wrapped in omentum and replaced in the abdomen (Table 10 and Figs. 62 to 65).

TABLE 10.—SERIES IV. THE EFFECT OF DECAPSULATION OF THE KIDNEY

Group 1.—Decapsulation of the kidney and wrapping it in omentum (thirteen experiments)

	Experiment	Animal	Date of operation	Duration of experiment, days	Decapsulation of kidney and wrapping in omentum	Decapsulation of kidney	Necropsy	Condition of cortex	Formation of capsule	Increase in capsular veins observed macroscopically	Decrease in capsular veins observed macroscopically	Increase in connectives tissue in cortex
1	(124)	B793	2–19–17	353	Left	.. ..	53	....	+	..	+	+
2	(286)	B900	3–24–17	203	....	Right	539	....	+	..	+	+
3	(591)	C114	8–24–17	169	....	Right	58	....	.....	..	+	+
						Left	...	....	+	..	+	+
4	(543)	C 82	8– 3–17	113	Right	Left	675	....	Right Left	+		+
5	(220)	B855	3–12–17	70	....	Right	333	....	+		+	+
6	(387)	B984	5– 7–17	51	....	Right	398	....	+	..	+	+
7	(398)	B985	5– 7–17	46	....	Right	387	....	+	..	+	+
8	(261)	B882	3–19–17	42	....	Right	293	....	+	+	..	+
9	(542)	C 81	8– 3–17	17	Right	Left	489	....	Right	..	+	
10	(538)	C 77	7–30–17	17	Right	Left	480	....	+	+	..	+
11	(98)	B768	2–10–17	7	Left	.....	77	Left congested				
12	(535)	C 74	7–30–17	3	Right	Left	447	Left congested Right not congested				
13	(537)	C 76	7–30–17	2	Right	Left	446	Right slightly congested Left congested				

TABLE 11.—SERIES IV. THE EFFECT OF DECAPSULATION OF THE KIDNEY

Group 2.—Decapsulation of the kidney and wrapping it in omentum and ligation of the renal artery or branches of the renal artery (seven experiments).

	Experiment	Animal	Date of operation	Duration of experiment, days	Decapsulation of kidney and wrapping in omentum	Ligation of renal artery	Ligation of one branch of renal artery	Necropsy	Formation of new capsule	Anastomosis renal and capsular arteries
1	(273)	C444	4–29–18	526	Right		Right	464	+	
2	(99)	B769	2–10–17	16	Left	Left		90	+	
3	(53)	B742	1–27–17	10	Left	Left		53	+	0
4	(398)	C529	6–17–18	348	Right		Right	261		
					Left		Left		+	0
5	(265)	C438	4–22–18	325	Right		Right	93	+	0
6	(364)	C505	6– 3–18	38	Right		Right	347		
					Left		Left		+	0
7	(235)	C412	4– 4–18	15	Right		Right	220	+	0

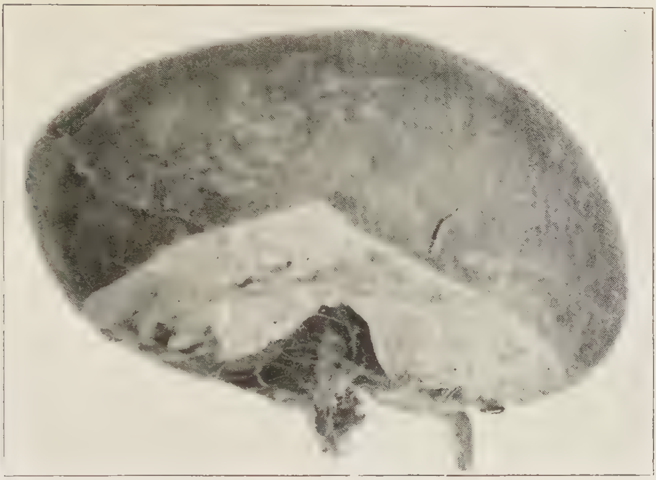

Fig. 62 (Series IV, Group 1, Experiment 7 [B 985]).—Decapsulation of the right kidney, wrapping in omentum, forty-six days' duration; formation of new dense, thick, fibrous capsule.

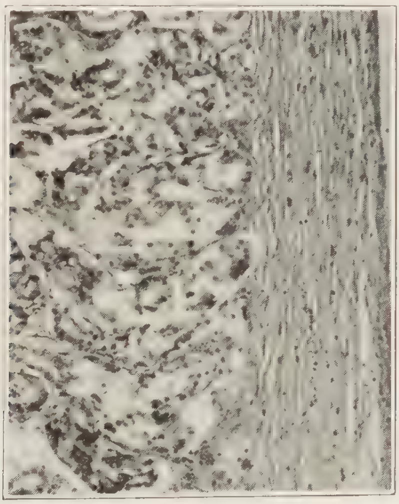

Fig 63 (Series IV, Group 1, Experiment 2 [B 985]).—Section of capsule of kidney shown in Figure 62.

The conclusions drawn from these experiments are that (1) the kidney forms a well marked new capsule in about seventeen days, (2) the interstitial tissue of the cortex increases, and (3) the newly formed capsule is more dense and fibrous and contains fewer (new) blood vessels than the normal capsule.

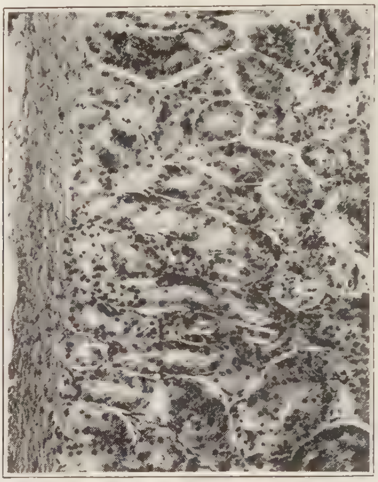

Fig. 64 (Series IV, Group 1, Experiment 4 [C 82]).—Decapsulation of right kidney, 115 days' duration; formation of new fibrous capsule closely associated with connective tissue of tubules.

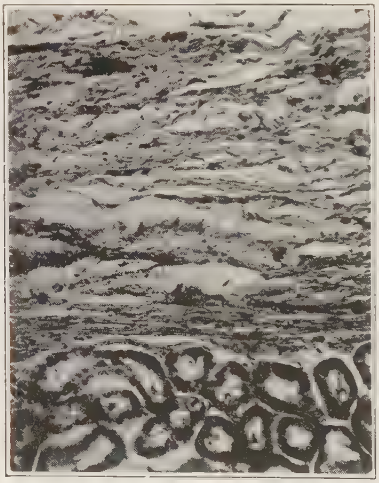

Fig. 65 (Series IV, Group 1, Experiment 1 [B 793]).—Decapsulation of left kidney wrapping in omentum, 353 days' duration; formation of a thick, fibrous capsule, associated with the intratubular connective tissue.

Group 2. Decapsulation of the kidney and wrapping it in omentum and ligation of the renal artery or branches of the renal artery (seven experiments).—In two experiments the renal artery was ligated and the decapsulated kidney wrapped in omentum, and in five one or more branches of the renal artery were ligated and the kidney decapsulated and wrapped in omentum (Table 11). These procedures had no effect on the production of atrophy, which indicates that the capsular vessels do not anastomose with the branches of the renal artery.

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TRANSPLANTATION OF THE KIDNEY AND THE OVARY*

CARLETON DEDERER

The author's purpose in making the research was to discover a method of obtaining a successful homotransplantation of the kidney and of the ovary. Prior to his work the literature did not show a completely successful homotransplantation of the kidney in the dog and no instance of successful transplantation of the ovary although ovarian tissue had been grafted successfully. Neither had the transplantation of a dog's kidney to its neck with successful removal of the other kidney been reported.

In Part I the successful autotransplantation of a kidney to the neck in a dog by anastomosis of the vessels of the neck to the renal vessels and the union of the ureter to the skin is described. The dog's other kidney was extirpated two weeks after the transplantation and the dog thrived, gained in weight, and lived one hundred twenty-five days; it then died from hydronephrosis. The ureter retained its function and even hypertrophied to such an extent that the periodic streams of urine at times squirted three feet away from the dog.

In Part II the homotransplantation particularly of the kidney and of the ovary in the dog is described. One of the cases described in detail is that in which a very small shepherd-collie puppy was operated on. A kidney and an ovary were removed from another puppy of the same litter and transplanted to the neck of the first puppy. The ovary as is generally the case in the dog received its blood supply from the renal vessels.

There was technical difficulties in this operation due to the small size of the renal artery which was less than 1 mm. in its outside diameter. However, end-to-end anastomosis was accomplished by suturing with raw silk fibers, and on needles from $1/4$ to $3/8$ inch long. The dog recovered and lived long enough to demonstrate the success of the experiment, which was terminated the twenty-seventh day by fatal distemper-pneumonia with ulcerative colitis. On the twenty-sixth day phenolsulphonephthalein was readily excreted from the kidney in the neck. During the night of the twenty-sixth day the intussusception was reduced by operation but did not avail to save the life of the dog.

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In all cases in which homotransplantation was unsuccessful in dogs not related even though the technical difficulties were overcome it was found that the transplants passed through a critical period from about the fifth to the eighth day; destruction by cytolysis then ensued.

In conclusion the author shows that in unrelated mongrel dogs no successful homotransplantation can be achieved, but if the dogs are related by birth successful homotransplantation of organs is possible.

EXPERIMENTAL CLOUDY SWELLING OF THE KIDNEY IN THE RABBIT*

W. RAY SHANNON

Virchow's conception of cloudy swelling as turbidity due to the presence of albuminous granules in the cytoplasm must be modified. The cloudiness and opacity of organs produced by acute infectious processes is seldom associated with an increase of albuminous granules. It is evident that cloudy swelling as commonly described includes more than one type of pathologic process. With this in mind, the study of experimental cloudy swelling of the kidney was undertaken with particular attention to the albuminous granules.

Rabbits were used exclusively in the experiments. Compensatory changes were studied by removal of the opposite kidney or ligature of its ureter. Cloudy swelling was produced by subcutaneous injections of tartaric acid, by placing sterile macerated liver in the peritoneal cavity, and by producing chronic suppuration in the subcutaneous tissues with pasteurella and proteus.

The results of fifty experiments are summarized as follows:

The normal rabbit's kidney always contains, in the convoluted tubules, coarse albuminous granules. Usually these granules are so numerous in a few tubules that they appear dark in the fresh tissue. The granules are apparently thin-walled vesicles filled with fluid. They are best fixed by solutions containing formalin. They are not fixed in solutions containing acetic acid.

When one kidney is removed the dark tubules are increased in the opposite kidney during the first twenty-four or forty-eight hours, but the increase of albuminous granules is not sufficient to cause any definite change in the gross appearance of the kidney.

Subcutaneous injections of tartrates produce a swollen, cloudy kidney, but there is no increase of albuminous granules. The cloudiness and swelling are apparently due to edema, anemia, tissue disintegration, and so forth.

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Intraperitoneal injections of autolyzed liver tissue produce a markedly cloudy and swollen kidney. The albuminous granules disappear entirely. The gross changes are apparently due to the same factors concerned in the tartrate experiments.

Chronic suppurative processes attended with marked emaciation cause an enormous increase of albuminous granules in the kidneys. These granules are often larger than the normal and irregular in shape, but they seem to have the same chemical composition.

Acute toxemias cause a rapid disappearance of the normal albuminous granules.

An acute toxemia superimposed on a chronic suppurative process causes a disappearance of the albuminous granules.

Kidneys which show an enormous increase of albuminous granules usually give a normal phenolsulphonephthalein output, and the cells are usually intact. This form of cloudy swelling is therefore probably not a degenerative change, but a physiologic response to an increase of protein waste products in the blood.

There is no relation between the formation of albuminous granules and fatty metamorphosis.

It is suggested that the term cloudy swelling be discarded and that the several processes producing this appearance be considered separately.

URANIUM NEPHRITIS*

ORVILLE N. NELSON

It has been maintained by Dickson and others that a renal lesion may be produced in animals with uranium nitrate, which is similar to chronic nephritis in man. Chronic nephritis in man is anatomically either a glomerulonephritis or an extensive arteriosclerosis of the kidneys. Glomerulonephritis begins as an inflammation of the glomeruli, either exudative or proliferative, which finally leads to partial or complete closure of the capillaries with subsequent hyalinization of the glomerulus. The tubule undergoes atrophy of disuse after the glomerulus ceases to function. Extensive arteriosclerosis of the kidneys is due to disease and the consequent changes characteristic of arteriosclerosis in the large and small arteries of the kidneys. The glomeruli and tubules undergo atrophy or necrosis. Any experimentally-produced lesion must correspond anatomically to one of these two diseases if it is to be considered similar to nephritis in man.

Spontaneous nephritis in rabbits does not resemble nephritis in man in any anatomic characteristics, but is characterized by lymphocytic infiltration in the renal tissue and atrophy of the tubules involved in the infiltrated areas. There is never any primary disease of the glomeruli or of the blood vessels. The descriptions given by Dickson indicate that the lesion which he obtained experimentally was similar to spontaneous lesions if not identical with them.

Fifty-four rabbits in which no trace of albumin was present in the urine were used, and, in order further to eliminate spontaneous lesions, an exploratory laparotomy was performed. If there were any abnormal appearances on the surface of the left kidney, the animal was not used. After this careful selection of the experimental animals, subcutaneous injections of uranium nitrate were begun.

Eighteen rabbits died within a few days after a comparatively large single injection. They showed the usual acute degeneration characteristic of uranium poisoning.

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* Abstract of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirement for the degree of Master of Arts, 1920.

Thirty-six rabbits were given repeated injections at short intervals over long periods. The duration of these experiments varied from six weeks to nine months. Fifteen rabbits were under experimentation more than three months, and six more than five months. Albuminuria was constantly present throughout practically every experiment. From nine to twenty injections of uranium nitrate were given in the experiments that lasted more than five months. Nine rabbits of this group showed occasional small lymphocytic accumulations such as are often seen in normal rabbits. One showed deeply pitted shrunken kidneys, but the anatomic structure in this case was that of ordinary spontaneous nephritis, and there was no resemblance to the forms of chronic nephritis found in man.

It is concluded that uranium nitrate does not produce a chronic nephritis comparable in any anatomic respects with chronic nephritis in man.

THE POSTNATAL GROWTH OF THE KIDNEY OF THE ALBINO RAT, WITH OBSERVATIONS ON AN ADULT HUMAN KIDNEY*

JOHN A. KITTELSON

A careful volumetric study of the cortex and medulla of the kidney with complete counting of the renal (Malpighian) corpuscles, was made on serial sections of the kidney of the albino rat at birth, and at one, two, three, seven and twelve weeks. The volumes of the cortex and of the medulla were also measured in an adult rat (thirty-five weeks). Also the volumes of the cortex and of the medulla were measured and the number of corpuscles estimated in an adult human kidney. The principal results are summarized as follows:

1. The postnatal growth of the cortex in the rat's kidney is fairly uniform, showing in comparison with the entire body a relative increase between birth and two weeks of age, decreasing slightly thereafter.

2. The growth of the medulla in the rat's kidney is more varied. The rate of growth of the medulla between birth and three weeks of age increases much more rapidly than the rate of growth of the cortex or of the entire body, and also decreases more rapidly thereafter. The characteristic curve of relative growth for the entire kidney, increasing to a maximum at three weeks and decreasing thereafter is therefore apparently due largely to the varying rate of growth in the medulla.

3. The volumetric ratio of medulla to cortex in the rat's kidney changes from 1:3.05 at birth to 1:2.91 at the age of one week; 1:2.02 at two weeks, 1:1.50 at three weeks, 1:2.10 at seven weeks, 1:2.00 at twelve weeks, and 1:2.87 in the adult. Linear measurements are inadequate to indicate the volumetric relations.

4. The total number of fully formed renal corpuscles found in the kidney of the newborn rat is 10,465, or 15,533 including those

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incompletely formed. The number increases to 19,682 at one week, or 26,598 including those which are not fully formed. At two weeks there are 24,061 (plus about thirty incompletely formed); 25,930 were counted at three weeks; 28,583 at seven weeks and 28,863 at twelve weeks.

5. The total number of corpuscles in the rat's kidney is apparently reached during the third postnatal week, as but few could be found in process of formation at the age of two weeks and none at three weeks or thereafter. The apparent slight increase in the total number of corpuscles at seven and twelve weeks is therefore probably due to individual variation.

6. The number of fully formed corpuscles for each cubic millimeter of cortex in the kidney of the rat decreases from 1057 (or 1586, including the incomplete) at birth to 131 at twelve weeks, and to 75 in an adult at thirty-five weeks.

7. The average diameter of the renal corpuscles increases from about 62 micra in the newborn to about 127 micra in the adult rat. There is an apparent decrease in the average size of the corpuscles at one and two weeks, due perhaps to a larger proportion of the small young corpuscles at these periods.

8. The total (relative) volume of the renal corpuscles forms about 13 per cent of the cortex, or 10 per cent of the kidney, in the newborn. Later the relative volume of the corpuscles decreases irregularly, forming at twelve weeks only about 6 per cent of the volume of the cortex or 4 per cent of the volume of the total kidney (both cortex and medulla).

9. In an adult human kidney, the cortex measured about 93,000 cu. mm. and the medulla 43,000 cu. mm. The number of corpuscles was estimated at 1,040,000, with a total volume of 4356.35 cu. mm., forming $^{1}/_{21}$ of the total cortical volume, or $^{1}/_{33}$ of the total kidney volume (both cortex and medulla)

THE PHENOL EXCRETION IN THE URINE OF INFANTS, INCLUDING THE NEW-BORN*

CHARLES U. MOORE

The urinary excretion of phenol in normal infants was determined by the colorimetric method of Folin and Denis. Some modifications were made. All flasks were filled to volume and placed in a water bath at 40° to 45° for about ten minutes, when they were ready for the colorimeter. In using the large test tubes placed within a tall 300 c.c. beaker, as Folin and Denis direct, it was found more satisfactory to use a wire gauze to support the test tubes about 3 cm. from the bottom. The top of each test tube extended over the side of the beaker and with the funnel in it became a perfect condenser, provided the water was not boiled too vigorously.

The urine of fifteen infants, of ages varying from one week to six months, was studied. In several cases the urine was tested daily for three successive weeks, during which time week-end rest periods of three days each were allowed. In all ninety-five twenty-four hour specimens were examined. The weights of these infants were from 1,765 gm., to 5,740 gm., the food intake from 405 gm. to 1,080 gm., and the stools from one to nine each day.

The urine of nineteen new-born infants was studied by means of 164 analyses of 114 specimens; each specimen included the urine passed during the first three days of life.

It was found that in infants aged from one week to six months, the total daily excretion of phenol varied from 9.0 mg. to 58 mg.; the average was 28.9 mg., of which 83 per cent was present as free phenol. The phenol excretion decreased with an increase in the number of stools. The breast-fed infant excreted less than the artificially fed infant. The greater the nitrogen intake, the greater the phenol excretion. Trebling the protein intake doubled the phenol excretion.

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Contrary to the earlier findings, phenol was always present in the urine of the new-born. It varied from 2.1 mg. to 23.4 mg.; the average was 11.2 mg. for the first three days of life; 76 per cent was free phenol. As phenol is present during this period, it must originate in part through endogenous metabolism.

INFECTIONS OF THE KIDNEY*

WILLIAM J. TUCKER

The frequency of surgical conditions of the kidney as a postoperative complication and its association with various septic conditions throughout the body make the early recognition of such infections very important. There are at present two generally recognized avenues of entrance of infection to the kidney (1) the hematogenous and (2) the ascending.

Lesions in various renal infections made it difficult to assume that the ascending mode of infection has any importance as a cause. If pyelitis and pyelonephritis were of ascending origin, cystitis would be found frequently. Colon bacillus is the predominating organism in infections of the kidney, while the staphylococcus is generally the infecting organism in the urethritis of children. The possibility of ascending infection is not denied, particularly if the protective mechanism at the ureteral orifice has been destroyed by disease.

It has been asserted that ascending infection travels through the lymphatics and not through the blood vessels. This statement is based on the facts that the veins of the bladder and ureter open into the general circulation and not into the kidney circulation, and that even when the lumen of the ureter is open to infection the organisms are not found in the mucosa but in the lymphatics. Moreover, if the lumen is experimentally closed the process extends to the kidney; but if the lumen is permitted to lie open and the lymphatics are closed, there is no ascending infection.

Focal infections often play an important rôle in disease of the kidney. The bacteria from the tonsils of one patient showed specific localizing effects in the kidney when injected into a rabbit. The bacteria differ markedly in the types of lesions produced. Cocci show marked predilection for the glomeruli and the Bacillus coli and the Bacillus tuberculosis for the convoluted tubules.

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Once given a foothold the organisms are specific in singling out the structures of the kidney for damage. The lesions in thirty-five of the present series of sixty-three cases were of the coccus type. In the removed kidneys cortical abscesses were found. The condition starts, not in multiple simultaneous infection throughout the kidney, but in the inflammatory reaction around the glomeruli from an embolic focus in the vessels. In the cortical abscess type, the kidney is usually enlarged, reddened and congested, and bleeds easily. In one case the abscess formation was so localized that in the hope of saving the lower and functioning half of the kidney, heminephrectomy was done. The part left behind functioned perfectly, as was demonstrated by ureteral catheterization, but the infection progressed and it was later necessary to remove the remaining portion.

When colon bacilli alone are present the kidney becomes enlarged, reddened and congested. A diffuse mottling is frequently present and no degeneration of tissue is found, as in the coccus infections. The invasion of the kidney from the pelvis, in the lesions caused by the colon bacillus, takes place along the lymphatics which run from the papillæ to the capsule and form a network around the tubules and blood-vessels. Processes at first are usually unilateral, but later become bilateral if surgical interference is not resorted to. Lesions that are bilateral in the beginning are usually a part of a general pyemia or septic endocarditis.

In the streptococcus group of renal infections of hematogenous origin, the lesions are in and around the glomeruli; in all cases the cocci show a marked specific affinity for the glomerulus and its convolutions. Hyperemia and edema of the interstitial tissue is also a marked feature.

The tuberculous type of lesion is often associated with a healed or active pulmonary lesion. The Bacillus tuberculosis, like the colon bacillus, tends to involve the glomerulus, but has an affinity for the convoluted tubule.

Two types of symptoms are recognized: (1) the fulminating or more virulent type, which usually proves fatal before any renal symptoms make their appearance, and (2) the nonvirulent type which tends to spontaneous recovery without any serious renal damage. The coccus group of renal infections are usually more virulent, while the colon type tends to assume the nonvirulent form. The attack may or may not be ushered in by a chill, and the temperature may range from 101 to 103°. Pain is a constant symptom referred to the kidney region. Muscular rigidity is a fairly constant finding and very frequently confusing. Costovertebral tenderness may be considered as a pathognomonic sign; but was observed in only 29 per cent of the cases that were later verified at operation.

The differentiation of the type of infection is important, as the colon bacillus infections are rarely surgical while the coccus infections invariably call for surgical interference. The chief points of difference are the toxemia and urinary changes; that is, the patients with colon infection are less toxic and show marked colon changes.

Conservatism is fatal in coccus infections as delay may endanger the life of the patient and the integrity of the other kidney. Tuberculosis of the kidney indicates a radical removal, since the majority of cases of tuberculosis of the kidney are unilateral in the beginning and tend to become bilateral. Urinary antiseptics act well in colon infections, but are ineffective in the coccus type or glomerulus type of infection. The keynote of the treatment of colon infection is conservatism, with medicinal measures to preserve the kidney function. In the coccus type of infection the only successful form of treatment is the radical surgical procedure.

RENAL ABSORPTION WITH PARTICULAR REFERENCE TO PYELOGRAPHIC MEDIUMS*

EDWARD H. WELD

The dangers incident to pyelography have resulted from (1) the use of insoluble mediums, (2) the use of mediums which are poisonous when absorbed, and (3) the injection of the mediums under too great pressure.

Dogs were used in all the experiments. The animal was anesthetized with ether and a lumbar incision was made by the usual surgical technic. The operation seemed to be facilitated if the lumbar region was elevated by means of a pad about 3 inches thick; this gave better exposure. The muscles were split down to the peritoneum, which was pushed forward; the ureter was located, drawn up, and ligated, care being taken not to disturb the blood-supply. The various solutions to be tested were then injected into the ureter, which was again ligated about 1 to 2 cm. below the pelvis of the kidney. The ureter was divided between the two ligations. The wound was then closed and x-rays taken immediately afterward and at various intervals as long as any shadow of the kidney pelvis could be noted.

The solutions were injected with a piston syringe. As a rule, from 1.5 to 2 c.c. were injected. It is known that this amount of fluid will penetrate somewhat into the tubules and that it will probably cause greater distention than if only enough to fill the kidney pelvis is used. As the same amount of all mediums was injected, however, it was thought that they could easily be compared by this method, even though the pressure was greater than would normally occur in pyelographic work. Furthermore, in ligating the ureter the work was not done under normal conditions. Nephrectomies were done on the animals at intervals of from one hour to thirty days and the specimens were studied microscopically. A few of the kidneys were removed at

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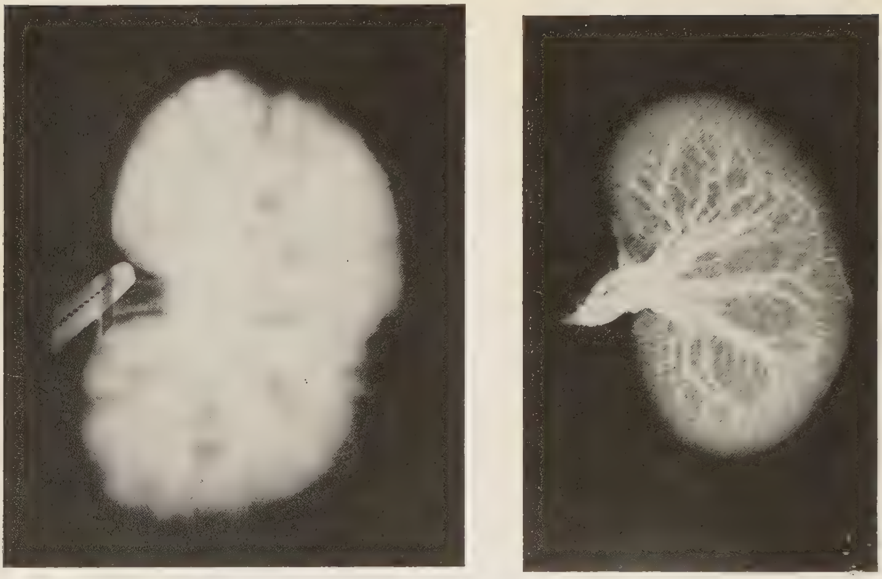
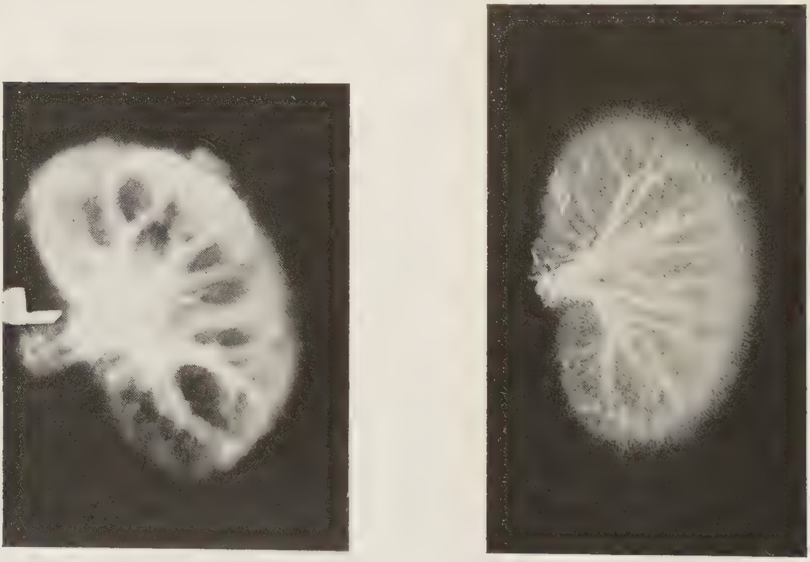


a *b*

Fig. 66.—Roentgenogram of an injection of the venous circulation of the kidney: *a*, sodium bromid solution; *b*, bismuth emulsion with condensed milk.



a *b*

Fig. 67.—Roentgenogram of an injection of the arterial circulation of the kidney: *a*, sodium bromid solution; *b*, bismuth and sodium bromid.

necropsy when the dogs died of intercurrent disease. A number of the kidneys were tested physiologically for the urinary secretory pressure and for absorption, and others were used in perfusion experiments.

Attempts to study the gradual development of hydronephrosis by pyelographic methods proved unsuccessful as the medium was absorbed from the pelvis of the kidney too quickly. The effect of pyelographic mediums retained in the pelvis of the kidney is most marked during the first hour after injection. There does not seem to be much difference in the effect on the kidney of retention of the different soluble pyelographic mediums. When the ureter is ligated these mediums are seldom retained more than one and one-half hours. This rapid absorption is apparently from the medullary portion of the kidney.

Studies on the toxicity of different substances used as pyelographic mediums showed that sodium bromid and sodium iodid are apparently innocuous when injected intravenously. Potassium iodid is very toxic because of the potassium ion. Thorium nitrate in 15 per cent solution varies greatly in toxicity, some samples being very toxic and some quite nontoxic.

Absorption of phenolsulphonephthalein and various soluble pyelographic mediums from one kidney and their appearance in the secretion from the opposite kidney in a short time were demonstrated. Further studies with phenolsulphonephthalein showed both secretion into the hydronephrotic kidneys and absorption from them. The degree of interchange is in proportion to the amount of medullary kidney tissue remaining, and, therefore, in inverse proportion to the amount of hydronephrosis. The medullary portion of the kidney is the first to be destroyed by hydronephrosis.

In studying the absorption of pyelographic mediums from the renal pelvis, it was shown that, although reverse perfusion can not be done from vein to artery, Locke's solution injected into the ureter at 120 mm. of mercury causes a dripping of the fluid from the vein under a pressure of 20 mm. If dyes, such as methylene blue, were added to the injected fluid they were found later in the medullary portion of the kidney. Studies with other solutions bore out these findings. X-ray examination after the injection of opaque substances into the arterial system showed the greater part of the injected capillaries in the cortxe; injection of the vein showed the greater part in the medulla (Figs. 66 and 67). Thus the kidney circulation may be conceived as represented by Fig. 68. All the fluid enters the kidney by the renal

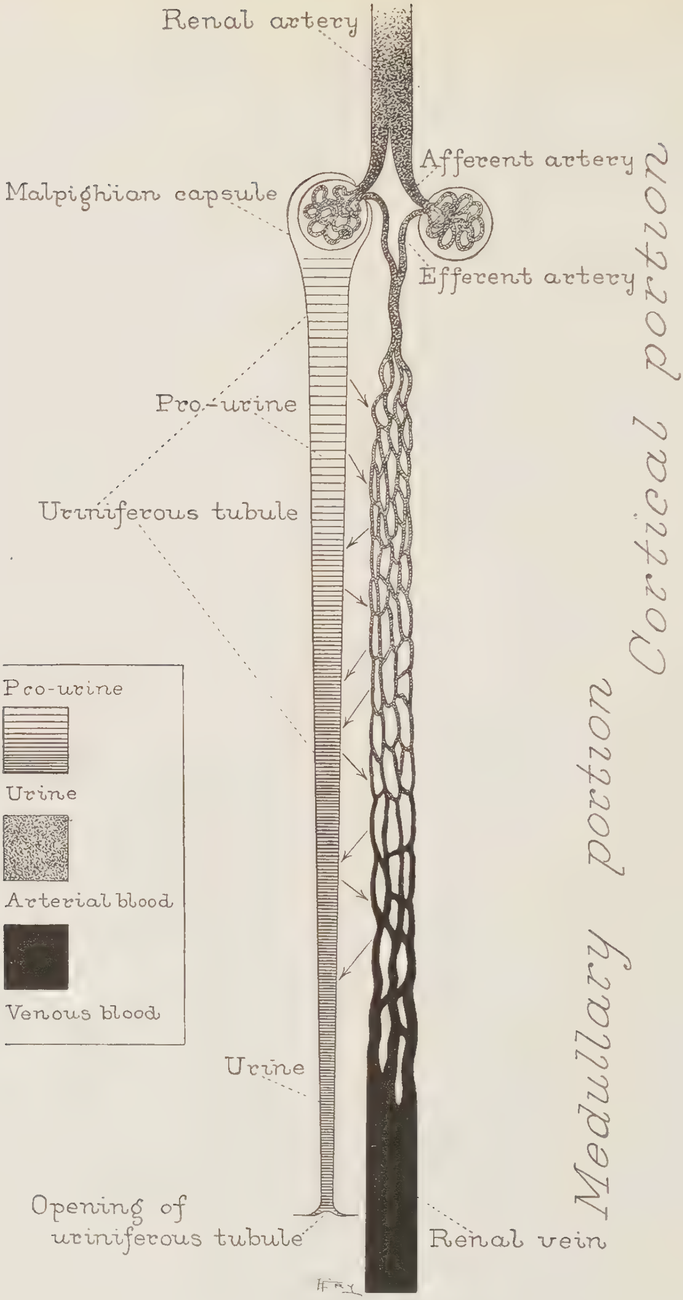


FIG. 68.—A diagrammatic conception of the "modern view" of urinary secretion.

artery from which part of it goes through the capillaries of the glomeruli and is then collected into smaller arteries. From this a second

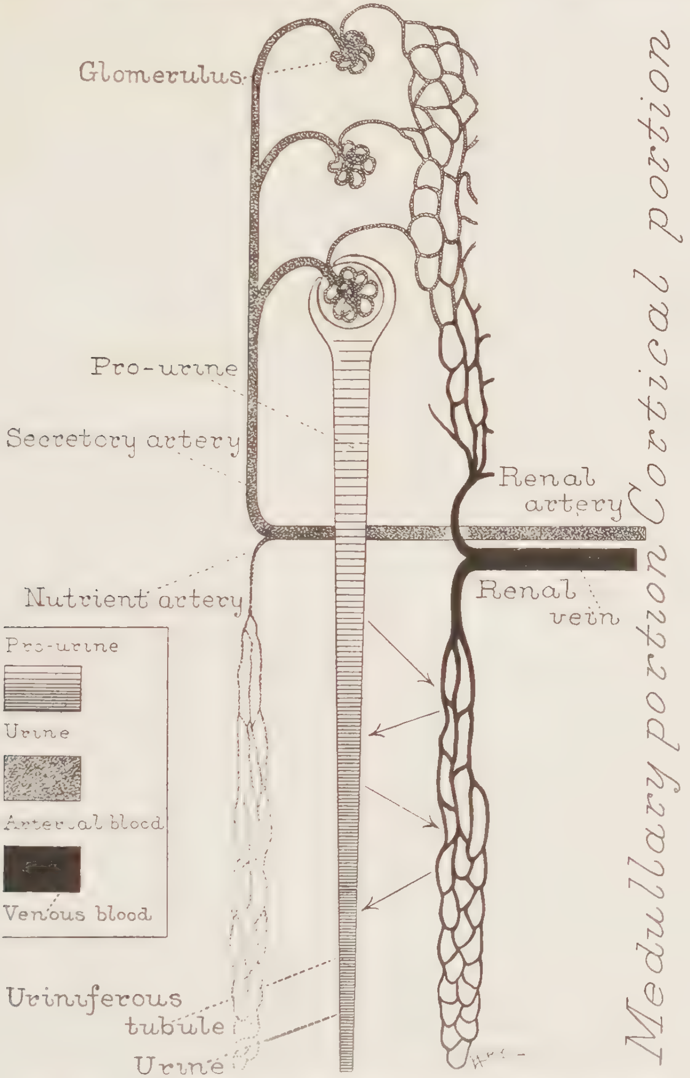


FIG. 69.—Diagram of absorption from the uriniferous tubule and the formation of urine.

set of capillaries springs which surround the tubules, and is then collected into the veins. The other part of the fluid, a serous portion, leaves the arterial system at the glomeruli and probably some at the convoluted portion of the tubules. This fluid is said to gain entrance into the tubules probably by physical processes and also by vital activity of the cells. The fluid, so-called glomerulous filtrate, travels down the tubules and is in a large part reabsorbed into the venous circulation either by vital activity of the cells or by physical processes. The part of it that is not absorbed escapes into the pelvis of the kidney as urine. Figure 69 illustrates the results that have been deduced from analysis of the experiments; it also shows the probable course of fluid when it is injected into the ureter and escapes from the vein.

These studies also show the possibility of the kidney acting as a focus of infection by allowing absorption of microörganisms into the blood stream. Unabsorbable mediums produce destruction of the kidney tissue. Colloid silver is very toxic on intravenous injection. Experiments with intra-ureteral injection of mediums under pressure showed that the break and extravasation of mediums from the pelvis usually take place at the poles. In view of this danger only nontoxic, sterile solutions should be used. Sodium bromid seems to fulfill all requirements as a practical pyelographic medium.

A STUDY OF THE ROENTGENOGRAPHIC FINDINGS IN RENAL TUBERCULOSIS*

FREDERICK A. OLSON

Early recognition of renal tuberculosis is desirable. It has been estimated by various observers that more than one-third (from 33.33 per cent to 50 per cent) of all suppurative diseases of the kidney are due to tuberculosis bacilli. Hence the great truth and importance of the statement made by Albarran many years ago: "Early diagnosis, early nephrectomy."

Bryan and Peters performed the first nephrectomy for tuberculosis of the kidney in the early seventies, but it has been left for men working in the last decade, especially in the last five years, to make the greatest strides in the refinements in this field of genito-urinary diagnosis.

The value of the roentgen ray in the diagnosis of tuberculosis of the urinary tract has not been generally appreciated. The first report of the roentgenographic findings in a tuberculous kidney was made by Strater in 1910. Soon after several articles appeared in foreign literature, and two appeared in American literature.

In a study of 709 cases of tuberculous kidneys on record in the Mayo Clinic, it was found that more than 20 per cent showed roentgen findings of value in differentiation. Every observer will welcome this aid particularly in conditions as follows:

1. If because of intolerance, contracted bladder or impassable stricture of the ureter, the cystoscopic findings are inadequate.
2. If the cystoscopic data are not typical of renal tuberculosis.
3. If the clinical findings are not suggestive of renal tuberculosis, or even of any involvement of the urinary tract, as may occur with a so-called autonephrectomy.
4. If in the presence of bilateral renal tuberculosis the typical shadows render cystoscopy or further clinical examination unnecessary.

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* Abstract of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Urology, 1918.

Shadows appearing in the roentgenogram caused by renal tuberculosis are of various forms. With the improved roentgenologic technic and with the typical shadows of tuberculosis in mind, even the more faint shadows may be useful in diagnosis. The irregular contour and varying density of the renal shadows is pathognomonic. Again they may be of lesser density throughout than those of renal stone. Such shadows in the renal areas may be classified into four distinct groups:

1. Multiple small scattered punctate shadows.

2. The more common form of irregularly rounded shadows of 1 cm. or more in diameter, usually in a polar area.

3. Larger, rounded, often lobulated, shadows showing the outline of the kidney entirely or in part.

4. A fourth type sometimes added, the so-called filigree type; a peculiar streak-like formation 0.5 cm. to 0.75 cm. in diameter.

Ureteral shadows are tube-like shadows, since they are irregular images of a part of the ureter usually the lower third.

Prostatic shadows are usually smaller and scattered throughout the gland. They vary from 2 mm. to 1 cm. in diameter.

Roentgenographs obtained by use of the various opaque mediums injected into the renal pelvis are at times necessary for a complete diagnosis.

Pyelograms, ureterograms and cystograms may identify and differentiate doubtful shadows. The characteristic pelvic deformities obtained in a pyelogram are (1) areas of cortical necrosis and (2) irregular inflammatory dilatation of the pelvis, as has been pointed out by Braasch in his treatise on pyelography.

Ureterograms showing multiple strictures are suggestive. Distinction from benign stricture or obscure stone is necessary and more information must be sought, particularly in the pelvic outline.

The diagnostic features available in a cystogram are a contracted bladder, a dilated lower ureter, or an enlarged internal bladder sphincter or posterior urethra.

CARCINOMA OF THE PROSTATE*
A CLINICAL STUDY

HERMON C. BUMPUS

The comparatively recent introduction of radium as a therapeutic agent has centered medical interest around the various aspects of the treatment of carcinoma of the prostate, and current literature abounds with reports of cases thus treated. Whereas formerly the frequency of the disease, the clinical findings, the results of its surgical treatment, and the prognosis were almost established facts which the occasional atypical case but served to emphasize, now the entire progress of the disease has become altered by the therapy and all the various phases of the disease are opened again to new investigation. Because of this fact it seems pertinent to emphasize a phase of the disease that has received less study then many other aspects. I refer to the occurrence of metastasis, the frequency of which does not seem to be fully appreciated. Although as early as 1854 Sir Henry Thompson reported a case of osseous metastasis from a primary growth in the prostate, Blumer fifty-five years later was able to collect only forty-three such cases from the literature. That the occurrence of metastasis is important no one will deny. That it may be present without producing symptoms and that it may be present when the gland is not appreciably or only slightly enlarged are facts which I wish particularly to emphasize, for unless the presence of such metastasis is carefully ruled out by thorough roentgenologic study, or, when the roentgenograms are negative, by careful neurologic examination, reports of results of any form of therapy in carcinoma of the prostate are subject to criticism, and deductions drawn from them are open to doubt. In order to call attention to these points a careful study has been made of the 362 cases of carcinoma of the prostate observed at the Mayo Clinic during the years 1914 to 1919 inclusive. Of these, seventy-nine

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* Thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Urology, 1920.

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(21 per cent) showed evidence of metastasis. A comparative study of the group with metastasis and of the group without metastasis forms the basis of this paper.

LYMPHATIC DRAINAGE OF THE PROSTATE

A study of metastasis necessitates a knowledge of the lymphatic drainage of the prostate. The belief that carcinoma of the prostate does not readily invade the lymphatics is probably due to a lack of such knowledge since it was not until 1902 that the several drainage routes in man were known (Cuneo and Marcille). In order fully to understand this drainage, the lymphatics of the pelvis must be studied. They consist of three main groups named from the great vessels about which they are situated: the external iliac glands, the internal iliac glands, and the common iliac glands.

"The lymphatics of the prostate arise by fine capillaries arranged in the form of a network around each glandular acinus. From these periacinous networks run larger vessels which pass towards the periphery of the gland and form at its surface a second network, the periprostatic network from which the collectors start to drain in four different directions. One collector starts from the posterior surface of the prostate and ascending on the posterior superior surface of the bladder, curves sharply outwards, crosses the internal iliac artery, and terminates in the external iliac group of glands midway between the crural arch and the bifurcation of the common iliac artery."

A second collecting trunk draining the posterior surface of the gland accompanies the prostatic artery and terminates in the internal iliac group. A third and a fourth set which arise from the posterior surface run downward and then upward across the lateral surface of the rectum, and ascend on the anterior surface of the sacrum, the shorter external trunks ending in glands of the internal iliac group situated internal to the second or third sacral foramen, and the larger internal trunks terminating in the common iliac group on the promontory of the sacrum. A descending trunk on the anterior surface of the gland, after uniting with vessels from the urethra, empties into the internal iliac group. The lymphatic glands of the external and internal iliac groups drain into the common iliac glands, which in turn empty into the abdominal aortic glands which constitute a continuous vertical chain (Fig. 70).

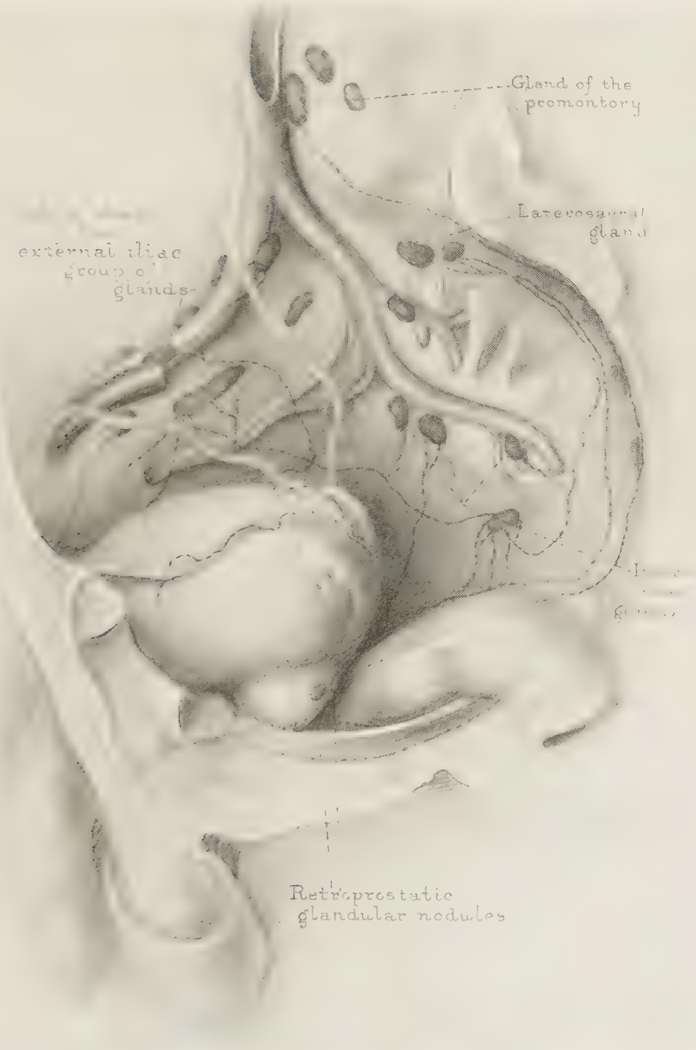
Gland of the promontory
Laterosacral gland
external iliac group of glands
Retroprostatic glandular nodules

FIG. 70.—Lymphatic drainage of the prostate gland and first lymphatics to become involved in carcinoma of the prostate.

METASTASIS TO THE GLANDS

It is apparent that glandular invasion from carcinoma of the prostate can be very extensive without giving physical signs, and that lymphatic involvement cannot be demonstrated until the glands have enlarged sufficiently to become palpable through the abdominal wall, or have increased to such size in the pelvis to be reached by the examining finger in the rectum. This knowledge possibly explains the discrepancy in the incidence of glandular involvement given by various authors. Young reported a series of 111 clinical and surgical cases with glandular involvement in but 20 per cent; he states that he believes these figures prove the infrequency of such involvement. Pasteau found glandular involvement at necropsy in 85 per cent of seventy-one cases; in 30 per cent the inguinal glands were involved. Kaufmann reports metastasis in 50 per cent of 100 necropsies found in order of frequency in the iliac glands, the inguinal glands, the glands of Scarpa's triangle, the axillary glands, the femoral glands, and the cervical glands.

In our series of 362 cases of carcinoma of the prostate metastasis was found in seventy-nine (21.8 per cent), in thirty-seven (10.2 per cent) the glands were involved (Table 1).

Table 1.—Metastasis in Glands

		Percentage of 79 patients with metastasis	Percentage of total number, 362 patients
Patients with metastasis in glands	37	46.1	10.2
Inguinal glands	20	25.3	5.5
Iliac glands	12	15.1	3.3
Cervical glands	9	11.3	2.5
Left cervical glands	7	8.9	1.9
Retroperitoneal glands	5	6.3	1.4

The low percentages of glandular metastasis noted clinically contrasted with the high percentages in postmortem reports indicate that glandular involvement occurs generally in the terminal stages of the disease. This is unquestionably true of involvement of the inguinal glands which probably occurs after that of all the deep lymphatics. The conclusion that glandular involvement is infrequent or late because of the low percentage of cases in which it is found clinically is erroneous, I believe, and if the iliac glands could be examined satisfactorily their early involvement would undoubtedly be proved. The fact that pain is often an early symptom of the disease, occurring as the first symptom in 34.1 per cent of our cases with metastasis, seems to point to early metastasis. The assumption is especially warranted when the pain is in the back, chest, or abdomen, where its occurrence can be explained only as pressure from metastatic growths on nerve roots and not as pressure from local extension, as in the case of sciatic, rectal, and perineal pains. Table 2 bears out this argument.

TABLE 2.—LOCATION OF PAIN IN TWENTY-SEVEN CASES OF CARCINOMA OF THE PROSTATE WITH METASTASIS

	Cases
Pain as first symptom	27
Thigh and back	5
Back	5
Thigh	4
Back and Chest	3
Rectum	2
Chest	2
Abdomen	2
Chest, back, and thigh	1
Chest and thigh	1
Thigh and inguinal region	1

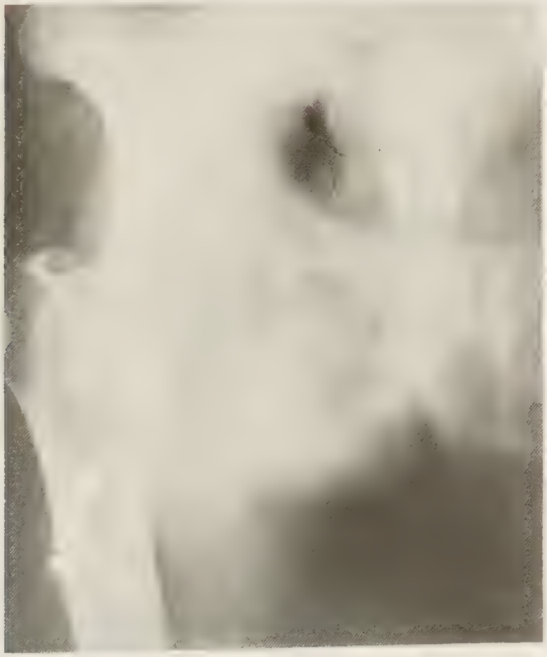

FIG. 71 (311469).—Roentgenogram showing destruction of ascending ramus of ischium from osteoclastic metastasis.

In many cases the pressure producing even this sciatic pain is probably not the result of an increase in the size of the gland, but of the pressure from the involved regional lymphatics on the sacral promontory. This fact is emphasized further by the numerous cases in which the roentgen ray failed to show any bony changes although the nerve root pains were so severe that they could be accounted for only on the grounds of pressure from involved glands along the sides of the vertebræ. In fact, it is extremely doubtful whether or not metastasis produces pain unless it exerts pressure on nerve roots or interferes with joint function. Several of our patients showed ex-

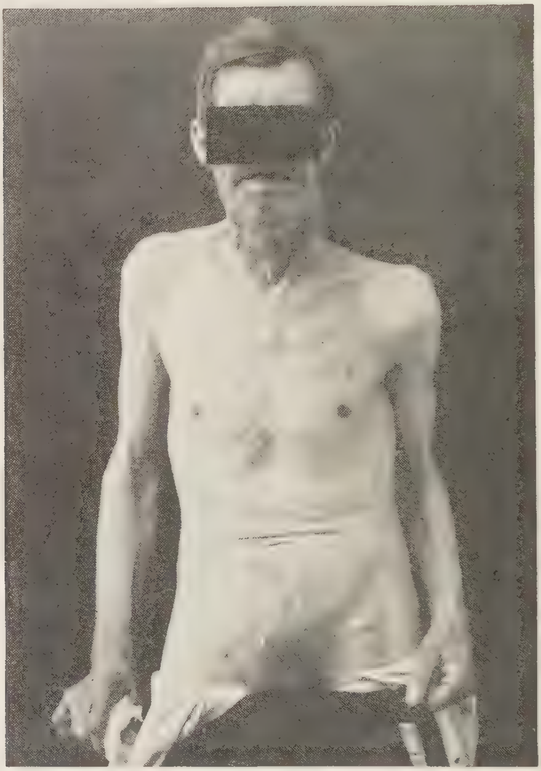

Fig. 72 (279878).—Marked metastasis to the inguinal and cervical glands and to the skin in a patient with carcinoma of the prostate. The patient's inability to close his mouth is due to edema of the tongue resulting from a mass of enlarged glands in the submaxillary region. Note the huge mass of glands in the left cervical region. An x-ray of the skeleton did not reveal any osseous metastasis.

tensive bony destruction but had no history of pain. In one case the entire ascending ramus of the ischium of the same side was destroyed (Fig. 71), but the patient complained of pain only when he moved the hip joint. Extensive glandular metastasis may also occur without pain; several of our patients who had no pain had iliac retroperitoneal and cervical metastasis. The general metastatic involvement shown in Figure 72 was painless until the cervical involvement (Fig. 73) had become so great that the lymphatic drainage to the tongue was blocked and the resulting edema caused the lower teeth to cut into the tongue's under surface. Pain is by no means a major symptom of the disease, as in our entire series its absence was noted oftener than its presence. As was expected it occurred more frequently in the cases with metastasis (75.9 per cent), than in those without (34.3 per cent), but even in one-fourth of the cases with metastasis the patients were free from pain. Table 3 gives the incidence of pain as a clinical symptom.

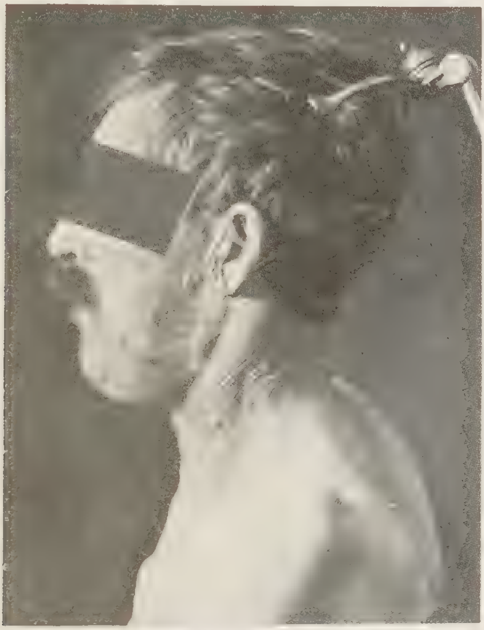

FIG. 73 (279878).—Enlarged glands in the left cervical region of patient shown in Figure 72. Metastasis to this group of glands occurred in 8.9 per cent of our cases with metastasis.

TABLE 3.—PAIN

Patients with metastasis with pain	60	(75.9 per cent of 79)
Patients with metastasis without pain	19	(24.1 per cent of 79)
Patients without metastasis with pain	97	(34.3 per cent of 283)
Patients without metastasis without pain	186	(65.7 per cent of 283)
Total number of patients with pain	157	(43.3 per cent of 362)
Total number of patients without pain	205	(56.3 per cent of 362)

PATHOLOGY

Cancer of the prostate may be primary in the gland; more frequently it is associated with simple hyperplasia. Judd found hypertrophy with cancer in 75 per cent of his cases, while Wilson and McGrath report their association in as high as 83 per cent of a series of cases. Whether the carcinoma in these cases is the end result of a transitional change beginning in the hypertrophied gland or a primary condition developing in conjunction with simple hyperplasia is a question which was first discussed by Albarran and Halle in 1891. They believed that carcinoma results from malignant degeneration in simple hyperplasia, and held that a definite relationship exists between the two conditions. They described a microscopic picture to which they gave the name of "epithelioma adenoid," which they believed represented various stages in this malignant degeneration, and reported its occurrence in 10 per cent of the prostates with benign lesions examined by them. Since their report has appeared however, other investigators have found similar cell masses in tissues which were unquestionably benign so that the theory is now generally discredited. Moreover, carcinoma nearly always develops in the posterior lobe although in some cases other lobes are the first to be involved in hyperplasia.

Two types of carcinomatous prostate.—Clinically, carcinoma of the prostate presents two fairly typical types of enlargement, although many intermediate types occur. In Type 1 the gland is so slightly enlarged and gives so few local symptoms that it is often discovered only because of symptoms produced by metastasis. Even in the late stages of the disease the local growth does not become extensive. The enlargement is generally uniform, without any of the irregularities of contour presented by the common type of carcinomatous gland. Characteristic stony hard areas are absent as a rule. Although there may be localized areas of greater density, the gland as a whole presents a lack of resilience rather than a stony hardness and resembles true inflammatory hypertrophy with which it is often confused, although in the latter case resilience is not lost. The gland is never so large that it cannot be outlined by the examining finger. In the more common type of carcinomatous prostate (Type 2) the gland may present any degree of enlargement according to the duration of the disease, but the topography encountered by the examining finger is always the same, irrespective of variations in size. The contour of the gland, palpated through the uninvolved rectal mucosa, is irregular, the surface is elevated at different points by masses, which, when examined individually, fail to give any sense of elasticity and have been characteristically described as of a stony hardness. These masses of carcinoma palpated through the normal or hypertrophic gland, compressed as a result of their growth, resemble nothing so much as the pit of a plum felt through the unripe fruit. As the disease advances these areas coalesce and the entire gland assumes this stony hardness, but if examination is made early in the disease, the involvement may be felt as individual areas. Because carcinoma of the prostate is primarily an infiltrating growth and produces destruction and necrosis only in its later stages, the localized growth becomes large. It spreads upward into the seminal vesicles beneath Denonvillier's fascia (which extends from the triangular ligament over the posterior surface of the prostate to the peritoneum as a tense fascial plane covering the prostate and vesicles), at first involving the soft tissues adjacent to the ejaculatory ducts and lower end of the vas deferens beneath the bladder trigone, and later invading the interior of the vesicles. This method of extension results in a unicornate or bicornate growth, depending on whether one or both vesicles are involved, often so large as to cause serious rectal obstruction, and in the terminal stages not only obstructing the bowel and making impossible any accurate determination of its extent by rectal palpation, but also involving the entire pelvis and often palpable suprapubically. The rectal and urethral mucosa is broken through only in the later stages, a fact which explains the very low incidence of hematuria. Only 1.3 per cent of our 362 patients named hematuria as a first symptom and it occurred grossly at any time in only 12.7 per cent.

The only means approaching accuracy in determining the percentage of occurrence of the two types of diseased glands is a classification in which the sizes of the glands are given on a scale of 1, 2, 3, and 4. All Type 1 glands are graded 1, and Type 2 glands are graded 2, 3, and 4. Naturally early cases of Type 2 glands are sometimes grouped with Type 1 glands. Type 1, size 1, glands were found in only 24 cases (6.6 per cent) of the series, Type 2, size 2 in 74 (20.4 per cent) size 3 in 93 (25.7 per cent), and size 4 in 110 (30.3 per cent); the size was not given in 16 cases histories. In the Type 1 glands, however, the disease metastasizes earlier and spreads more rapidly than in the larger glands.

Microscopic examination.—Microscopically, carcinoma of the prostate presents varied pictures, but microscopically as well as clinically in the two types are all intermediate gradations. Specifically the neoplasm is an adenocarcinoma. In the Type 1 carcinomatous prostate the cancer cells are scattered throughout a somewhat increased fibrous stroma and show almost no tendency to glandular formation. Figure 74 illustrates this tendency to infiltrate throughout the gland and shows how closely this type of carcinoma resembles scirrhous carcinoma of the breast from which, unless the origin of the specimen is known, it is difficult to distinguish. The Type 1 gland is far more malignant than the more frequent Type 2. This is evidenced clinically by the percentage of occurrence in cases with pain as the first symptom if pain is considered the result of metastasis. Size 1 glands occur on an average in 6.6 per cent of all cases and almost twice as often (11.1 per cent) in the cases with signs of early metastasis, that is in which pain is the first symptom. Sections from Type 2 glands show cuboidal columnar, and undifferentiated cancer cells crowding poorly formed gland acini, and in places breaking through into the stroma, where they collect in groups of undifferentiated cancer cells. Even in such groups, however, are found attempts at acinus formation (Fig. 75).

Radium therapy.—There is little doubt that of the two types the smooth, firm, well encapsulated carcinoma, which on rectal examination because of its small size seems to present ideal conditions for obtaining gratifying results with radium therapy, offers the graver prognosis. Probably better results may be obtained from treating the larger type of growth prior to the occurrence of metastasis which takes place late in such cases. Even when the small gland is treated early, it is doubtful whether so good a result may be obtained as in the large gland because of the potential malignancy of the cancer cells in the former.

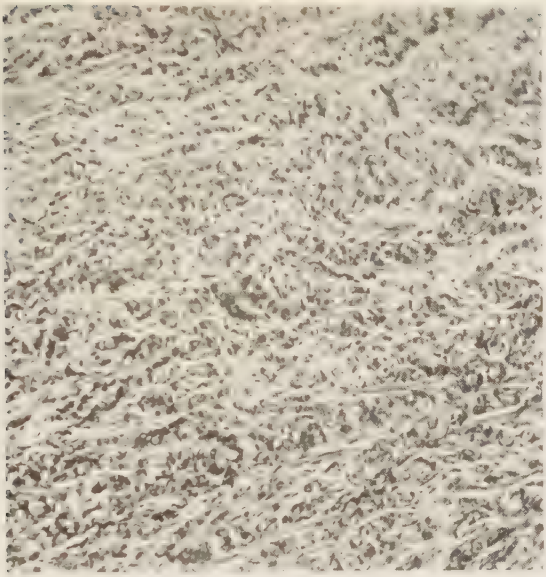

Fig. 74 (20348).—Photomicrograph of section from highly malignant Type 1 adenocarcinoma of the prostate of infiltrating type, exhibiting little tendency to glandular formation, but infiltrating through the stroma.

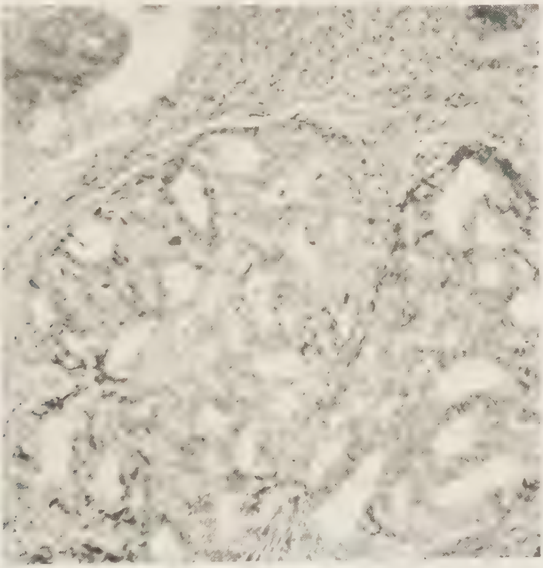

Fig. 75 (38264).—Photomicrograph of Type 2 adenocarcinoma of the prostate. Note the tendency of the carcinoma cells to atypical acinus formation and slight tendency of neoplasm to invade surrounding tissue.

METASTASIS TO THE BONES

The first case of metastasis to the bone in carcinoma of the prostate was reported by Thompson, in 1854. The patient, a man of 60, complained chiefly of frequent and difficult urination. Within a few months paraplegia developed gradually and finally resulted in loss of all sensation up to the armpits. Postmortem examination showed the prostate to be involved in a carcinomatous mass the size of an orange. Some of the adjacent glands were also involved. The right kidney was pyonephrotic, apparently the result of pressure on the lower ureter. A metastatic growth was found adherent to the first dorsal vertebra with similar small growths in the lower vertebræ which accounted for the paraplegia. In the second case, reported by Silcock, in 1884, metastasis to the femur resulted in spontaneous fracture and deposits in the cranial bones, producing central nervous

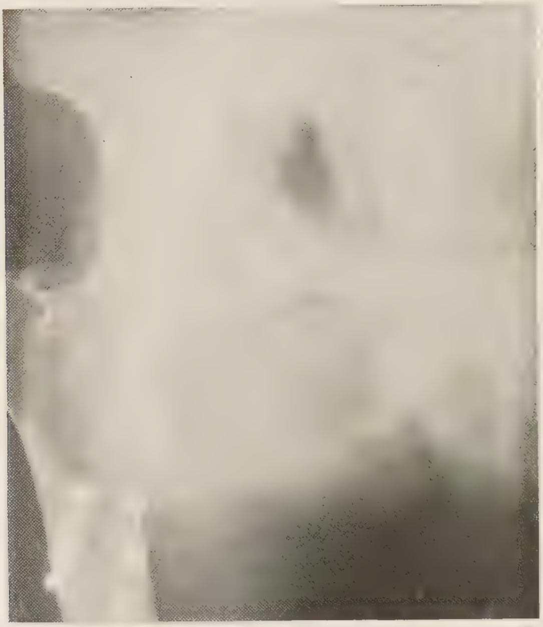

FIG. 76 (311469).—Roentgenogram showing destruction of the right ischium as a result of metastatic growth in which the osteoclastic tendency predominates.

system manifestations. Two of the patients in our series suffered spontaneous fractures of the femur late in the disease.

Osteoplastic and osteoclastic metastasis.—The first complete work on metastasis to the bone in carcinoma of the prostate was published by von Recklinghausen, in 1871. He compared the bony metastasis with fibrous ostitis and showed that the process is primarily an infiltration and so resembles inflammatory changes that he felt justified in terming it "carcinomatous ostitis." He called attention to the fact that metastasis begins in the medullary portion of the bone and spreads out, and that new bone formation is always more prominent, while the destructive character of the tumor remains in the background. We know this to be true in the majority of cases, but that osteoclastic changes may also occur is shown in Figures 71 and 76 which illustrate the complete destruction of much of the ischium. The patients complained of no urinary symptoms, and the very small, smooth, hard prostates were discovered only as a result of routine rectale examinations. The roentgenogram shown in Figure 76 was made in order to rule out the possibility of metastasis as the etiologic factor in a unilateral sciatica.

von Recklinghausen reported six cases of metastasis in his series, naming the vertebræ, femur, pelvis, ribs, sternum, skull, fibula, radius, and ulna in order of involvement. Blumer, in a collective report of the cases recorded in the literature up to 1909 and two of his own (forty-three cases) tabulated the frequency of involvement of the bones as follows:

	Cases
Vertebræ	35
Ribs	30
Pelvis	26
Femur	25
Skull	18
Sternum	16
Humerus	15

Since these cases represent necropsy findings they are of little value from a clinical standpoint, for there is no doubt that osseous metastasis occurs in the majority of cases.

Carlier and Davrinche give an incidence of osseous metastasis which approaches that in our cases:

	Cases
Vertebræ	17
Pelvis	13
Femur	11
Ribs	8
Sternum	8
Head	6
Humerus	6
Scapula	6
Tibia	3
Clavical	2
Fibula	1
Radius and ulna	1

These authors first called attention to the more nearly accurate statistics of the incidence of metastasis which may be expected from roentgen rather than from clinical examination. As was anticipated, the x-ray findings have been most useful in determining the extent of the lesion. Stewart believes that in the majority of cases the primary growth can be diagnosed by the roentgenographic appearance of the metastasis. He quotes from Phemister:

"Metastasis in bony structure following a primary carcinoma usually assumes the characteristics of the original growth; if the stroma predominated in the primary lesion, we are sure to have a condensing or osteoplastic form of metastasis; if the primary cancer were of a medullary form, we would have a secondary rarifying or osteoclastic process."

Stewart calls attention to the fact that in carcinoma of the prostate the stroma predominates, and a condensing form of secondary lesion should occur. This is in keeping with von Recklinghausen's findings and applies to the majority of cases, but as is evident from Figs. 71 and 76 osteoclastic metastasis also occurs.

Incidence and location.—Metastasis to the bone was found in forty-one of our patients who were x-rayed; they represent 51 per cent of the seventy-nine patients with metastasis, and 30.3 per cent of the 135 patients who were given a roentgen examination.

From Tables 4 and 5 it is apparent that the pelvis, the spine, and the femur (Figs. 77, 78, 79, 80, 81, and 82) are most frequently the site of metastasis. Pulmonary involvement is rare and occurs late in the disease. All three patients in whom metastasis was found in the lungs had pelvic and spinal inolvement, and in two the ribs, and in one the femurs were also involved (Fig. 83).

Table 4.—Incidence of Metastasis in 135 Patients X-rayed

Metastasis in pelvis	30 (37.5 per cent of 80 pelves x-rayed)
Metastasis in spine	24 (35.8 per cent of 67 spines x-rayed)
Metastasis in femur	6 (31.2 per cent of 16 femurs x-rayed)
Metastasis in ribs	6 (6.9 per cent of 86 ribs x-rayed)
Metastasis in lungs	3 (3.4 per cent of 86 lungs x-rayed)

Table 5.—Seventy-nine Patients with Metastasis

Metastasis in pelvis	30 (73.1 per cent of 41 pelves x-rayed)
Metastasis in spine	24 (66.6 per cent of 36 spines x-rayed)
Metastasis in femur	6 (66.6 per cent of 9 femurs x-rayed)
Metastasis in ribs	6 (19.3 per cent of 31 ribs x-rayed)
Metastasis in lungs	3 (9.7 per cent of 31 lungs x-rayed)

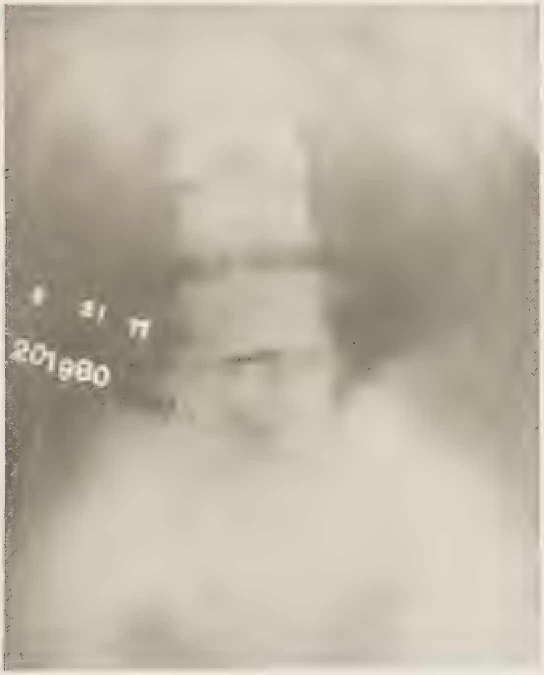

Fig. 77 (201980).—Metastasis to lumbar vertebræ and pelvis.

The figures in these tables also demonstrate that if the spine, the pelvis, and the femurs are rayed routinely in all cases of disease of the prostate suspected of being malignant, the number of cases of metastasis that will not be discovered will be negligible. It seems unneces-

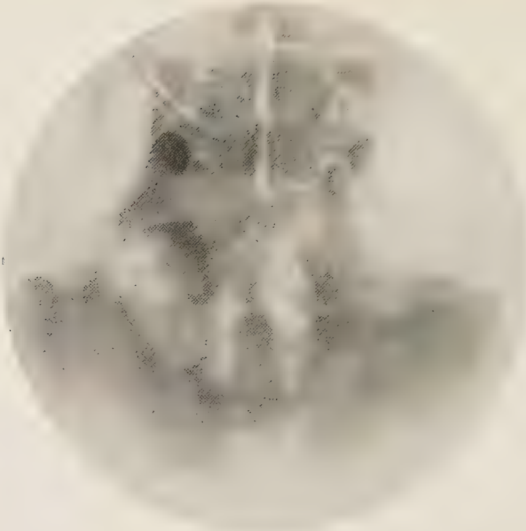

Fig. 78 (282420).—Multiple areas of metastasis in the sacrum and ilia; a common type of metastasis.

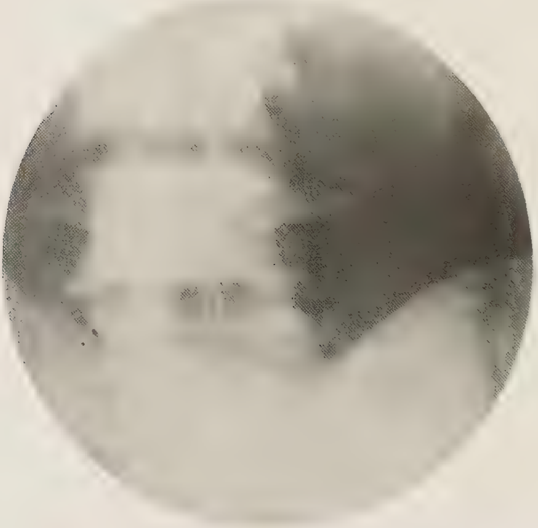

Fig. 79 (195263).—Metastasis to the lumbar spine, pelvis, and sacrum.

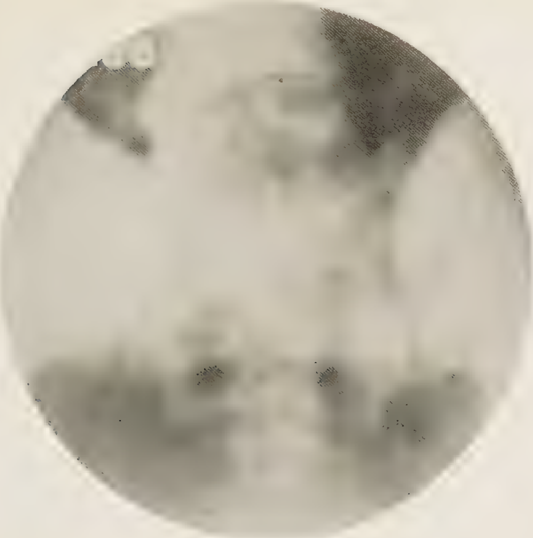

FIG. 80 (181438).—Extensive metastasis to the lumbar spine, sacrum, and ilia.

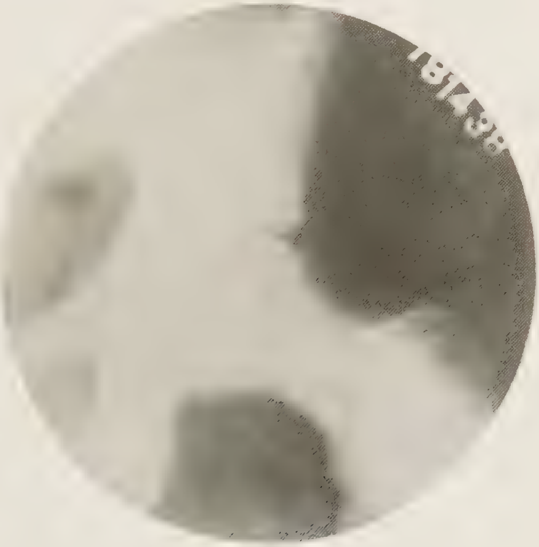

FIG. 81 (181438).—A condensing form of secondary lesion with extensive osteoplastic metastasis to the pelvis and femur.

sary to ray the lungs as a routine procedure since metastasis to the lungs only probably never occurs.

A comparison of the number of cases in this series with glandular metastasis with the cases with osseous metastasis leads to erroneous conclusions, for many patients who had marked glandular involvement were sent home as incurable without being rayed. For this same reason the percentages of occurrence of metastasis are based on the number of patients rayed rather than on the total number of patients. It seems conservative, therefore, to state that 30.3 per cent, or practically one-third of all patients with carcinoma of the prostate, will be found to have osseous metastasis, and in the overwhelming majority of this number metastasis will be found in the pelvis, the spine, and the femurs. Moreover, unless these areas have been carefully rayed, it is useless to draw conclusions on the efficacy of radium treatment or the results of surgery. In seventeen of our cases the spine and the

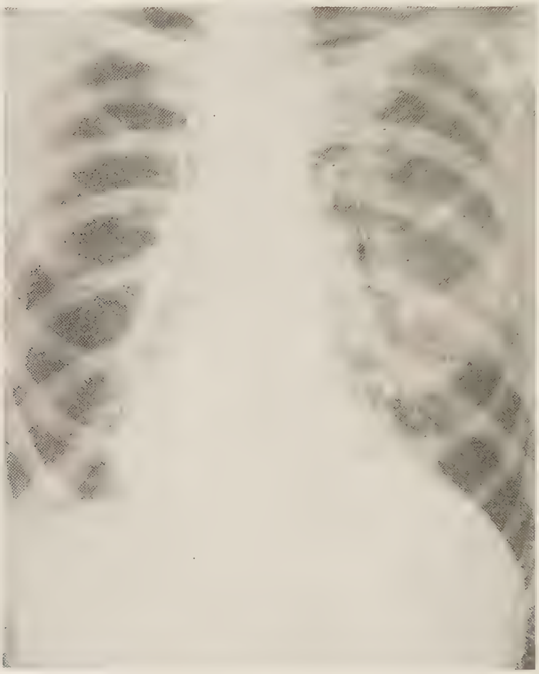

FIG. 82 (288379).—Metastasis to the ribs.

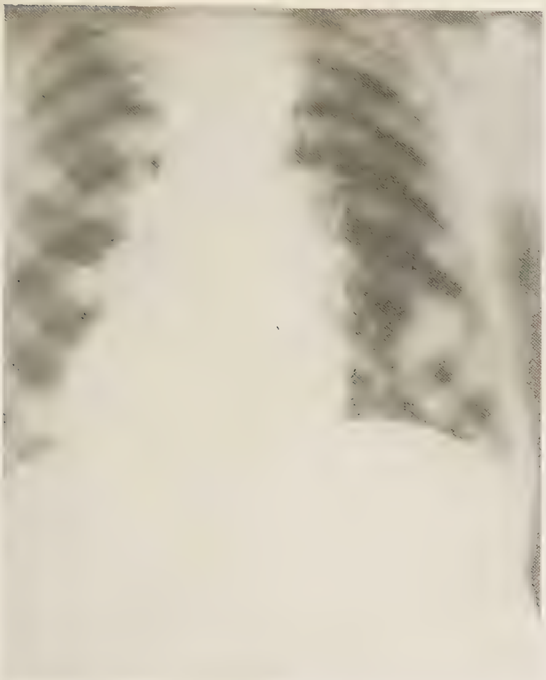

FIG. 83 (194448).—Area of metastasis to right lung.

pelvis were both involved; in twenty-one cases the pelvis was involved with some other structure. Table 6 shows the structures involved in the cases in which metastasis was found in one location only.

TABLE 6.—LOCATION OF METASTASIS IN FORTY CASES WITH SINGLE METASTASIS

	Cases
Pelvis	9 (11.3 per cent)
Inguinal glands	7 (8.8 per cent)
Cervical glands	5 (6.3 per cent)
Spinal cord	5 (6.3 per cent)
Iliac glands	4 (5.06 per cent)
Spine	3 (3.7 per cent)
Ribs	2 (2.5 per cent)
Femurs	2 (2.5 per cent)
Retroperitoneal glands	1 (1.2 per cent)
Skin	1 (1.2 per cent)
Liver	1 (1.2 per cent)

Spinal cord involvement.—Spinal cord involvement occurred in eight of our cases. In four of these the prostate was described as large and nodular, and the cord symptoms occurred late in the disease.

In one case history description of the gland was omitted. In the three other case histories the gland was definitely described as slightly if at all enlarged and of regular contour. In two of these cases pain of a neuralgic character in the chest, particularly about the shoulders, was the first symptom, followed in a short time by a gradually developing paraplegia. There was no urinary disturbance until after the sphincter control was lost as a result of the lesion of the cord. In the third case in which the patient gave a history of prostatic trouble of several years duration, pain about the hips preceded the paraplegia by a few weeks. In none of the three cases could any evidence of osseous involvement be demonstrated by the x-ray. The clinical picture was that of spinal cord tumor, and only after carefully ruling it out was the primary source of the malignancy found. These cases illustrate how such metastasis may produce pain simulating intercostal neuralgia or aneurysmal pains, and it therefore becomes an important point in the differential diagnosis of chest pains to include metastasis from carcinoma of the prostate. In fact, neuralgia or rheumatic pains developing during "the prostate age" in men who give no previous history of rheumatic infection should excite suspicion, and the prostate gland should be examined even if there is no suggestive urinary history. Pain was foremost in the list of first symptoms and appeared in 34.1 per cent of the seventy-nine cases with metastasis; while in the group of cases without metastasis pain had third place among the first symptoms and occurred in only 12 per cent of the 283 cases. From this it is apparent that lack of a suggestive urinary history by no means rules out the possibility of cancer of the prostate, and that in a third of the cases in which metastasis is found, the first symptoms are not referable to the urinary tract (Table 7).

TABLE 7.—FIRST SYMPTOMS

	79 patients with metastasis		283 patients without metastasis
Pain	27 (34.1 per cent)	Frequency	104 (36.7 per cent)
Frequency	22 (27.8 per cent)	Difficulty	92 (32.5 per cent)
Difficulty	13 (16.4 per cent)	Pain	34 (12.01 per cent)
Nocturia	9 (11.3 per cent)	Nocturia	24 (8.4 per cent)
Incontinence	2 (2.5 per cent)	Retention	9 (3.1 per cent)
Edema of the legs	2 (2.5 per cent)	Hematuria	5 (1.7 per cent)
Enlarged inguinal glands	1 (1.2 per cent)	Incontinence	1 (0.35 per cent)
Pyuria	1 (1.2 per cent)	Weakness	1 (0.35 per cent)
Retention	1 (1.2 per cent)	Loss of weight	1 (0.35 per cent)
None	1 (1.2 per cent)	Pyuria	1 (0.35 per cent)
		None	11 (3.5 per cent)

CLINICAL DATA

The absence of macroscopic hematuria as a first symptom in the cases with metastasis compared with its occurrence in only five of a large series of cases without metastasis is striking. Another noteworthy difference is the occurrence of retention as a first symptom in only one case with metastasis and in nine cases without metastasis. These two differences are undoubtedly attributable to the same cause, namely, the tendency of the carcinoma in cases without metastasis to grow locally, producing obstruction, and finally eroding the urethral mucosa, while the small gland (Type 1) found oftener in the cases with metastasis produces little obstruction and results in death from metastasis before erosion has occurred. When the urinary symptoms are studied alone throughout the disease, the same probable causes and general deductions become apparent. Retention occurs in 25 per cent of the cases with metastasis and in 33.9 per cent of the cases without metastasis. Macroscopic hematuria, which was entirely absent as a first symptom in the former group, appears as a later symptom in twice as many cases without metastasis as with metastasis. These facts show conclusively the nature of the two types of carcinoma of the prostate, the one exhibits a tendency to remain localized and produce urinary symptoms while the other quickly spreads to various parts of the body, with little tendency to localized growth, and results in death from metastasis. Eleven and one-half per cent of the patients with metastasis have no urinary symptoms in comparison with 3.8 per cent of the patients without metastasis (Table 8).

Table 8.—Urinary Symptoms

	75 patients with metastasis	283 patients without metastasis
Frequency	52 (65.8 per cent)	183 (64.6 per cent)
Difficulty	43 (54.4 per cent)	188 (66.4 per cent)
Retention	20 (25.6 per cent)	96 (33.9 per cent)
Nocturia	14 (17.7 per cent)	74 (26.1 per cent)
Hematuria	6 (7.6 per cent)	40 (14.1 per cent)
Incontinence	5 (6.4 per cent)	17 (6.1 per cent)
None	9 (11.5 per cent)	11 (3.8 per cent)

Although hematuria occurs microscopically twice as often in cases without metastasis, urine analysis fails to confirm this point, for blood is detected microscopically in the same percentage (32 per cent) of cases in both groups. Its absence, however, is noted twice as often as its presence. Table 9 also demonstrates the greater freedom from urinary disturbance of the patients with metastasis, normal urine being found in 46.8 per cent, as compared with 35.91 per cent of the patients without metastasis. The occurrence of pus, always the best index to urinary disturbance, is 11.52 per cent higher in the cases without metastasis.

Table 9.—Urinalysis

	75 patients with metastasis	283 patients without metastasis
Urinalysis	47 (59.19 per cent of 79)	181 (63.95 per cent of 283)
Blood in urine	15 (31.91 per cent of 47)	58 (33.91 per cent of 171)
Without blood in urine	32 (68.09 per cent of 47)	113 (66.08 per cent of 171)
Pus in urine	23 (48.93 per cent of 47)	107 (60.45 per cent of 177)
Without pus in urine	24 (51.06 per cent of 47)	70 (39.54 per cent of 177)
Negative urine	22 (46.8 per cent of 47)	65 (35.91 per cent of 181)

The differences in the findings of the two groups are confirmed by the amounts of residual urine found; the average in the cases with metastasis was 3.7 ounces, in the cases without metastasis, 6.9 ounces, still further evidence of the greater tendency to urinary difficulty in the latter group.

The age of the patients and the duration of the disease correspond closely to the statistics of other authors. Walker gives the average age as sixty-five years. In our series it was sixty-four and eight-tenths years; the average age of the patients with metastasis was 63, and of those without metastasis 66. The age of one patient was not given. The ages by decades were as follows:

Patients from 40 to 49 years	10 (2.7 per cent)
Patients from 50 to 59 years	78 (21.6 per cent)
Patients from 60 to 69 years	185 (51.2 per cent)
Patients from 70 to 79 years	80 (22.1 per cent)
Patients from 80 to 89 years	8 (2.2 per cent)

The average duration of life of the patients the date of whose first symptoms and date of death were definitely known was three and one-half years. The duration of the disease in patients with metastasis and in patients without metastasis and with reference to the type and size of the gland is based on data obtained from patients who were not treated surgically or with radium. Fenwick estimated the average at three years. The average duration of disease of our forty-one patients with metastasis who were traced was two and seven tenths years, of the 171 patients without metastasis, three and four-tenth years (Table 10). This slight difference is suggestive but not convincing of a greater duration of life of patients in whom metastasis is not found on examination. The length of time is probably much the same for the majority of patients with carcinoma of the prostate (Table 11), and metastasis probably occurs ultimately in all cases. The type of gland, not the presence of metastasis, determines the course of the disease (Table 12), and in cases with Type 1 glands the duration of the disease is undoubtedly shorter, due to the early metastasis. Because of the infrequency of this type of gland we have been able accurately to determine the duration of the disease in but three cases, a number too small from which to draw conclusions.

TABLE 10.—AGE OF 362 PATIENTS AND DURATION OF DISEASE WITH REFERENCE TO METASTASIS

Average age of 362 patients	64.5 years
Average age of 79 patients with metastasis	63.0 years
Average age of 283 patients without metastasis	66.0 years
Average duration of disease in 16 untreated patients with metastasis	2.73 years
Average duration of disease in 71 untreated patients without metastasis	3.4 years

TABLE 11.—DURATION OF DISEASE IN NINETY-TWO UNTREATED PATIENTS

Less than 1 year	8 (8.69 per cent)
1 year or more	21 (22.82 per cent)
2 years or more	15 (16.23 per cent)
3 years or more	15 (15.21 per cent)
4 years or more	3 (3.26 per cent)
5 years or more	9 (9.78 per cent)
6 years or more	1 (1.08 per cent)
7 years or more	1 (1.08 per cent)
10 years or more	4 (4.32 per cent)
Not given	16 (17.39 per cent)

TABLE 12.—SIZE OF GLANDS IN 215 UNTREATED PATIENTS ON A SCALE OF 1, 2, 3, 4

		79 cases with metastasis	136 cases without metastasis	Cases traced	Duration of disease
Size 1	11(5.1 per cent of 215)	8(10.1 per cent of 79)	3(2.2 per cent of 136)	3	2 years, 11 months
Size 2	36(16.7 per cent of 215)	14(17.1 per cent of 79)	22(16.2 per cent of 136)	13	4 years, 4 months
Size 3	48(22.3 per cent of 215)	17(21.5 per cent of 79)	31(22.8 per cent of 136)	19	3 years, 2 months
Size 4	74(34.4 per cent of 215)	19(24.1 per cent of 79)	55(40.4 per cent of 136)	33	3 years, 4 months
Size not stated	46(21.4 per cent of 215)	21(26.5 per cent of 79)	25(18.4 per cent of 136)	25	

CONCLUSIONS

1. Metastasis to the glands probably occurs more frequently in cases of carcinoma of the prostate than is demonstrable clinically because of the inaccessibility of the glands first involved.

2. Two distinct types of carcinoma of the prostate are distinguishable clinically and microscopically.

3. The smaller type of carcinoma of the prostate gives clinical and microscopic evidence of greater malignancy.

4. The larger type of carcinoma of the prostate tends to remain localized, resulting in more urinary symptoms and producing metastasis later in the disease than the smaller clinical type.

5. The larger clinical type of carcinoma of the prostate is more amenable to radium therapy because of its lesser potentiality of malignancy.

6. One-third of the patients with carcinoma of the prostate have osseous metastasis demonstrable by the roentgen ray.

7. The pelvis and spine are the most frequent sites of osseous metastasis.

8. Metastasis occurs rarely in the lungs, probably never without involvement elsewhere.

9. Metastasis to the spinal cord from carcinoma of the prostate closely simulates primary cord tumors and often occurs when the prostate is but slightly enlarged.

10. Pain is absent in one-fourth of all cases with metastasis.

11. Urinary symptoms are absent in 11.5 per cent of all cases with metastasis.

12. Neuralgic and rheumatic pains in men above middle age, even in the absence of urinary symptoms, should suggest the possibility of carcinoma of the prostate.

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THE EFFECTS OF ACUTE AND CHRONIC INANITION ON THE DEVELOPMENT AND STRUCTURE OF THE TESTIS IN THE ALBINO RAT*

DAVID M. SIPERSTEIN

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The immediate and the remote effects of inanition on the young organism are subjects of interest and importance, especially at the present time. Experimental studies in this field have yielded much of importance to biology in general and to medicine in particular. It is very desirable to know more about the changes produced in the sex glands of malnourished or undernourished infants and children, and the resulting effects on the reproductive system in later adult life. Inanition in adults may also occur either alone or associated with acute or especially with chronic wasting diseases, causing degenerative processes in the sex glands. Recent work on vitamine deficiencies (by McCarrison, Allen, Dutcher, and others) indicates that the changes produced in the sex glands by this partial inanition resemble those found after general inanition. A study of the changes occurring in the histologic structure of the testis of the albino rat during experimental inanition at various ages was therefore undertaken, and the results are embodied in the present paper.

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MATERIAL AND METHODS

A large part of the material for this investigation was presented to me by Dr. C. M. Jackson, to whom I am also indebted for constant advice, aid, and criticism throughout the course of the study. The material comprises the testes of several albino rats (*Mus norvegicus albinus*) that had been subjected to inanition experiments in the Institute of Anatomy. The adult animals during acute inanition were allowed water only; but one of the adults was placed on total inanition, as were also the young rats (two days old) which were removed from the mother and given neither food nor water. Those on chronic inanition were fed restricted amounts of Graham bread soaked in whole milk for various periods. Some were refed fully after underfeeding for various periods. The animals were killed by chloroform and necropsied, the testes being weighed (without the epididymis) and portions fixed for histologic study. For convenience the material at my disposal is grouped as shown in Table 1. In the first column, representing the individual rat numbers, the letters indicate the series (those necropsied by myself are 'Si'), the number following indicates the litter, while the number after the decimal point identifies the individual rat.

The testes had been fixed in either Zenker's, Bouin's, or Flemming's fixatives. Paraffin sections were cut at 2 to 10μ in thickness. The sections were stained chiefly with hematoxylin and eosin, Weigert's iron hematoxylin counterstained with van Gieson's stain, or Heidenhain's iron-alum hematoxylin counterstained in some instances with orange G or acid fuchsin. In general, Heidenhain's iron-alum hematoxylin without any counterstain gave by far the best results.

My own material was fixed in Carnoy's mixture (No. 1) and in Bouin's fluid. Fixation for one hour with Carnoy's mixture was found to be best. Sections were stained with Heidenhain's iron-alum hematoxylin with or without counterstain (acid fuchsin). This gave clear-cut karyokinetic figures in all stages of mitosis.

A number of measurements of cross sections of tubules were also taken from the stained sections by means of a micrometer eyepiece.

Table 1.—Individual Number, Age and Condition, Gross Body Weight and Weight of the Testes in the Albino Rats Used for Histologic Study

Rat number	Age, Diet	Final body weight	Weight of testes	Per cent of body weight	Average diameter of tubules	Average diameter of nuclei of interstitial cells
Group I.—Normal controls						
		gm.	gm.	%	Micra	Micra
Si 1.4	Newborn	5.1	0.0029	0.027	37.2	7.1
Si 2.5	4 days	7.1	0.0061	0.085	42.1	7.1
Si 1.2	4 days	7.0	0.0045	0.064	41.3	
Si 1.3	7 days	9.1	0.0200	0.219	50.5	6.9
Si 1.5	14 days	14.7	0.0780	0.529	65.3	
Si 6.0	21 days	20.6	0.0920	0.446	99.7	4.7
K 8.1	30 days	26.0	0.1154	0.443	88.1	
Si 12.1	35 days	38.7	0.2895	0.748	210.3	
Si 7.1	43 days	36.2	0.3940	1.088	235.0	
Si 5.2	56 days	77.0	......	.....	222.4	
Si 10.1	56 days	48.2	0.5460	1.112	175.7	4.5
Si 11.1	63 days	58.3	1.0030	1.720	204.5	4.6
Si 8.2	70 days	140.0	2.6930	1.923	257.8	
S 14.0	450 days	314.0	2.7545	0.877	323.7	4.5
Group II.—Acute inanition in rats from two days after birth						
Si 1.1	Starved 48 hours	4.01 (loss 25%)	0.0043	0.107	34.9	
Si 2.3	Starved 40 hours	4.21 (loss 21%)	0.0051	0.121	39.5	
Si 2.6	Starved 50 hours	4.10 (loss 25%)	0.0045	0.109	40.7	7.0
Group III.—Held at constant body weight by underfeeding from three weeks of age						
St 9.36	Maintenance diet 21–51 days	30.5	0.0958	0.31	100.3	
St 12.71	Maintenance diet 21–67 days	21.2	0.1056	0.50	95.9	4.8
S 7.31	Maintenance diet 21–70 days	31.4	0.3310	1.05	141.8	3.6
S 7.32	Maintenance diet 21–71 days	28.8	0.2100	0.73	102.8	
S 11.65	Maintenance diet 21–73 days	22.5	(R) 0.1860	0.83		
			(L) 0.0496	0.22	75.6	3,7
Group IV.—Retarded by underfeeding for long periods from three weeks of age						
St 44.1	Underfed 21–223 days	63.9	1.097	1.72	89.7	4.1
St 44.7	Underfed 21–418 days	40.9	1.187	2.90	91.2	4.4
St 44.4	Underfed 21–428 days	47.0	1.2968	2.75	120.4	4.3
M 29.109	Underfed 70–314 days	68.7	1.099	1.58	196.2	4.4
Group V.—Adult acute inanition						
S 25.0	Starved 9 days	198.3 (loss 35%)	1.479	0.75	234.2	4.9
S 26.0	Starved 8 days	171.5 (loss 39%)	1.905	1.11	216.3	4.3
S 27.0	Starved 8 days	219.0 (loss 30%)	2.430	1.11	267.3	
Si 9.1	Starved 11 days	114.0 (loss 47%)	1.468	1.28	168.5	4.2
Group VI.—Refed after underfeeding from three weeks to age indicated						
St 12.53	85 days. Refed 3½ days	44.9	0.2010	0.45	98.7	4.2
St 10.26	96 days. Refed 14 days	86.3	0.2672	0.31	123.4	5.3
S 12.52	109 days. Refed 37 days	117.4	1.1848	1.01	223.7	6.5
S 33.118	346 days. Refed 206 days	219.0	2.5182	1.14	291.1	

Sections of each testis containing the largest number of tubules cut in cross-section were chosen. In each section all the tubules showing a true cross-section (approximately circular) were measured. The results embodied in Table 1 are, therefore, the average of measurements of a variable number of tubules, ranging from eight to forty-four in the individual cases. While the observations are relatively few in number, they are sufficient to indicate clearly any marked change in size.

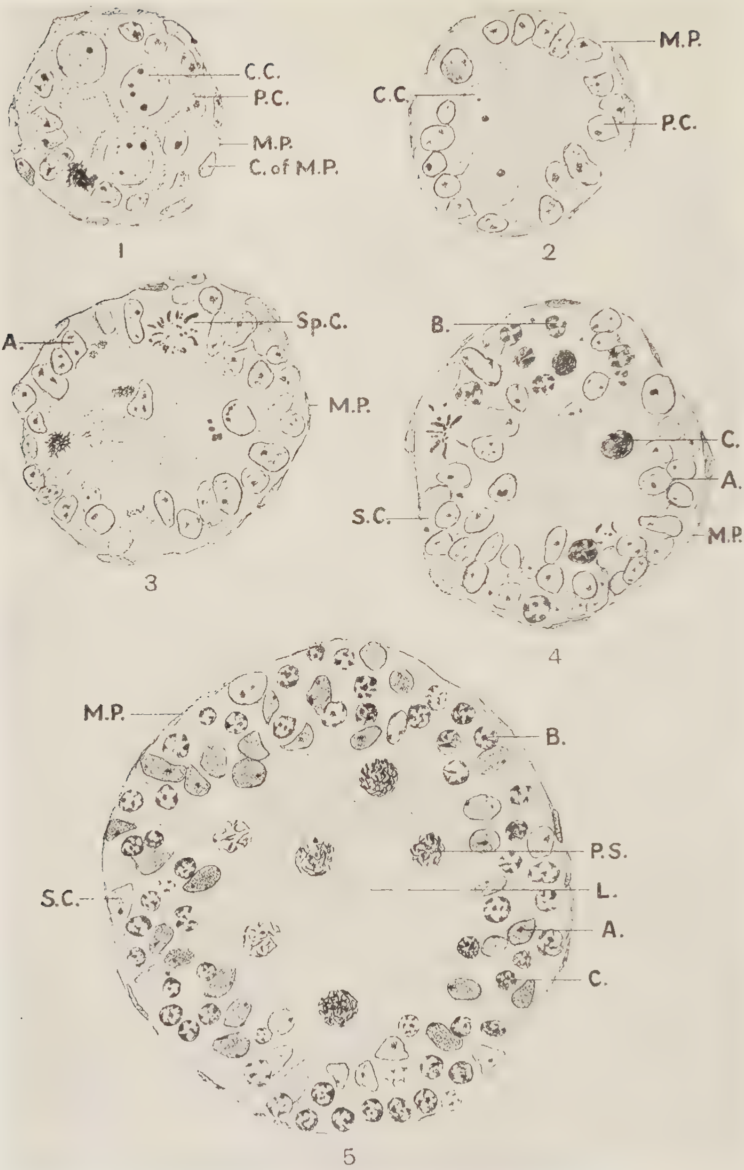
In addition, a few (ten to fifteen) nuclei of the interstitial cells in both the control and the test rats were measured at various stages and the averages calculated. Only a sufficient number of testes was taken from each group to determine whether any marked change in the size of the nuclei had taken place as a result of the test conditions. The results are listed in Table I. Measurements of the cell body were not attempted, on account of the irregularity of form. Measurements on the seminiferous epithelial cells were likewise found to be impracticable.

OBSERVATIONS

NORMAL POSTNATAL HISTOGENESIS OF THE TESTIS (GROUP II)

In order to understand more fully the changes which inanition produces in the testis, it is essential to review briefly its normal histologic structure and histogenesis as a basis for comparison.

Newborn (Fig. 84).—In microscopic sections of the testis in the newborn rat, the seminiferous tubules appear closely packed together at the periphery of the testis, while in the center of the section the tubules are less compactly arranged. The tubules average 37.2μ in diameter. The intertubular spaces contain many small capillary vessels and mesenchymal cells. The tubules themselves consist chiefly of a single layer of parietal epithelial cells, which apparently correspond to those designated as 'Sertoli cells' by von Ebner (1902) in the testis of the colt. These cells fuse to form a syncytium. Lumina have not yet appeared in the tubules. The central portion of each tubule contains from one to three large clear cells, each containing a definite, well-marked nucleus. Each nucleus has from one to three small clumps of chromatin situated usually (but not always) close to the periphery of the nucleus. These masses probably represent chromatin nucleoli. These large central cells apparently correspond to those described by von Ebner (1902) as the primitive germ cells ('Ursamenzellen') from which the spermatogonia are probably derived.



Figs. 84, 85, 86, 87, and 88.

EXPLANATION AND LEGENDS

The drawings were made with the aid of a camera lucida. The unit of magnifcation is 630 diameters or all the figures, with the single exception of Figure 93 (10), which has a magnification of 127 diameters. All the material stained with Heidenhain's iron-alum hematoxylyin had been fixed in Carnoy's fluid (No. 1). The remaining material had been fixed in either Bouin's or Zenker's fixatives.

Figures 84 (1) to 90 (7) show normal development in the epithelial wall and the growth of the tubules in albino rats from birth to eight weeks of age. All × 630.

Figures 91 (8) to 96 (13) show changes in the seminiferous epithelium and size of the tubules brought about by experimental conditions.

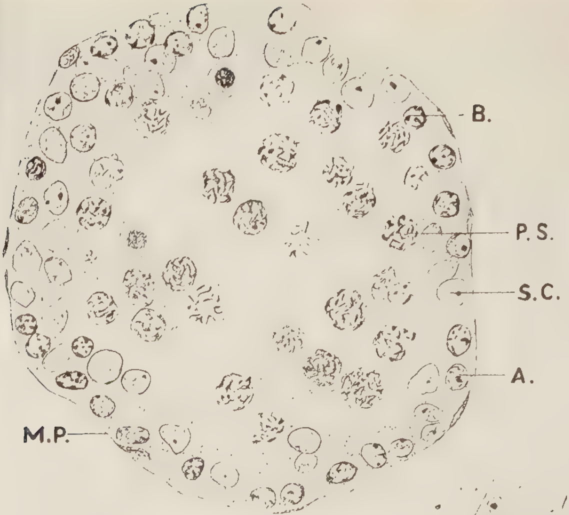
FIG. 84 (1).—Transverse section of a tubule from the testis of a normal newborn rat (Si 1.4). Section 6μ thick; stained with iron-alum-hematoxylin and acid fuchsin. × 630. Note the presence of a single layer of parietal cells, *P.C.*, and the large central cells, *C.C.*, in the center of the tubule. Each tubule is surrounded by a membrana propria, *M.P.*

FIG. 85 (2).—Transverse section of a tubule from the normal testis at four days (Si 2.5). Section 6μ thick; stained with iron-alum-hematoxylin. × 630. The number of parietal cells, *P.C.*, has increased, while the central cells, *C.C.*, are less frequent. Membrana propria, *M.P.*

FIG. 86 (3).—Transverse section of a tubule from the normal testis at seven days (Si 1.3). Section 6μ thick; stained with iron-alum-hematoxylin. × 630. Mitotic activity is apparent. A spermatogonium in metaphase is well shown, *Sp.C.* Germinative cells are all alike (Allen's type A). Membrana propria, *M.P.*

FIG. 87 (4).—Section of a tubule from the normal testis at fourteen days (Si 1.5). Section 6μ thick; stained with iron-alum-hematoxylin and acid fuchsin. × 630. Cells of (Allen's) types A and B are abundant and a few cells of type C are present, *A.*, *B.*, *C.* Sertoli cells, *S.C.*, are beginning to assume their adult position and structure. Membrana propria, *M.P.*

FIG. 88 (5).—Section of a tubule from a normal testis at twenty-one days (Si 6.0). Section 10μ thick; stained with iron-alum-hematoxylin. × 630. All types of cells, *A.*, *B.*, and *C.*, are present. Primary spermatocytes, *P.S.*, have appeared. Sertoli cells, *S.C.* Membrana propria, *M.P.* Note the formation of a lumen, *L.*, in the tubule.



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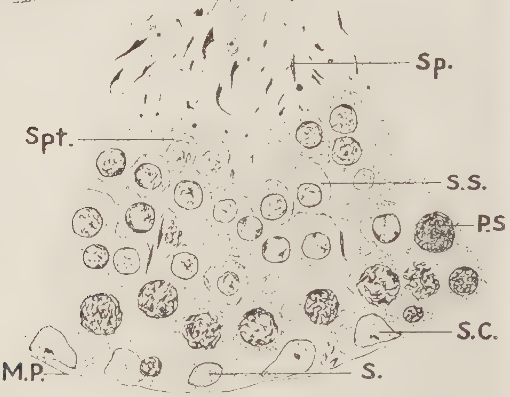

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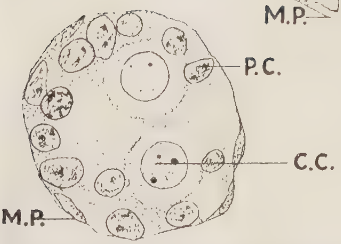

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Fig. 89 (6).—Section of a tubule from a normal testis at four weeks (K 8.1). Section 10μ thick; stained with iron-alum-hematoxylin. × 630. Presents the same picture as the preceding figure, but also shows a marked increase in the number of primary spermatocytes, *P. S.*

Fig. 90 (7).—Portion of a transverse section of a tubule from a normal testis at eight weeks (St 5.2). Section 10μ thick; stained with iron-hematoxylin. × 630. Note the gradual transition from the spermatogonia to the mature spermatozoa. This corresponds very closely to the condition found in the adult testis. Sertoli cell, Interstitial cells (of typical structure) have not yet developed. There is present, however, in the intertubular tissue a peculiar type of cell which appears to be the forerunner of the later interstitial cells (Fig. 97, A). This cell contains a large round nucleus (average diameter, 7.1μ) extremely rich in chromatin, which in turn is surrounded by a narrow rim of clear cytoplasm. By the form of its nucleus and its deeply staining chromatin, it is easily distinguished from the ordinary young mesenchymal or connective-tissue cell.

Fourth day (Fig. 85).—In a normal rat at four days of age the development of the testis has advanced considerably. The whole section is filled with seminiferous tubules (average diameter, 41.7μ). Within the tubules themselves the parietal cells show no material increase in number, but the spermatogonia (Allen's cell type A) have appeared. They are probably derived from the central cells ('Ursamenzellen' of von Ebner), which still occur (less numerously) and present mitoses, though less frequently than in the newborn. Before dividing, they often appear to migrate from the center of the tubule toward its periphery and crowd in among the parietal cells. Some tubules already contain a few cells which resemble Allen's type B; that is, a primary spermatocyte cell in its earliest phase. The forerunners of the interstitial cells are beginning to group themselves together in the intertubular spaces.

One week (Fig. 86).—A section of the testis from an albino rat at seven days shows an increase in the number and size of the tubules (average diameter, 50.5μ). (The larger number of tubules appearing in a cross-section of the testis may, however, be due to an increase in the length of the tubules rather than an actual increase in their number.) This represents the earliest stage described by Allen (1918). The tubules now contain two or three layers of cells. Very few central cells still remain, but spermatogonia (Allen's type A) are present in large numbers. There are very few type B cells. In other words, an undifferentiated condition of the spermatic epithelium still prevails.

S.C.; spermatogonia, *S.*; primary spermatocytes, *P.S.*; secondary spermatocytes, *S.S.*; spermatids, *Spt.*; spermatozoa, *Sp.*; membrana propria, *M.P.*

Fig. 91 (8).—Section of three tubules from the testis of a rat four days old (Si 2.6) which had been subjected to acute inanition for fifty hours. Section 6μ thick; stained with iron-alum-hematoxylin and acid fuchsin. × 630. Note that the structure resembles that of the newborn more closely than that normal at four days. Compare with Figures 84 (1) and 85 (2). Central cells, *C.C.*; parietal cells, *P.C.*; membrana propria, *M.P.*

The syncytium (Sertoli syncytium) which fills the tubules at this stage is exceptionally well shown. The number of mitotic figures has again increased, so there are now as many figures in the field as there were at birth. The interstitial cells are more numerous and the amount of interstitial tissue is increased.

Two weeks (Fig. 87).—There is a large increase in the apparent number of seminiferous tubules, and their average diameter has increased to 65.3μ. There are many cells of types A and B, and some tubules even show Allen's type C (spermatocytes in which the chromatin masses become more diffuse than in type B and assume a 'woolly appearance'). A few cells have advanced as far as the leptotene stage. It is now fairly easy to distinguish between Sertoli cells and spermatogonia. The Sertoli cell has a nucleus with only a little chromatin material, in this way differing from the nucleus of the spermatogonium, which has a large amount of deeply staining chromatin.

Three weeks (Fig. 88).—Lumina are just beginning to appear in the closely packed tubules, whose average diameter has now increased to 99.7μ. Spermatogonia, cells of types A, B, and C, are numerous. A few tubules already contain primary spermatocytes showing mitotic figures. In many places, degenerating primary spermatocytes and spermatogonia are also present. This appears to be a normal physiologic process, occurring in the testis at all ages. No secondary spermatocytes or spermatids are to be seen. The interstitial tissue is assuming its adult structure (Fig. 97, *B*). The nuclei average only 4.7μ in diameter, which is much smaller than at birth (7.1μ).

One month (Fig. 89).—The testis at this stage shows only a slight advance in development. It is distinguished by the large number of primary spermatocytes present. Spermatids have not yet appeared. The interstitial tissue shows no change.

Six to ten weeks.—Sections of testes from forty-three to seventy days of age show a gradual increase in the size of the tubules (Table 1) and in the number of mature sperm elements. Mature spermatozoa appear for the first time at the age of forty-three days. Their number increases so rapidly that at eight weeks (Fig. 90) the histologic structure of the testis differs in no important respect from that in the older rats. The interstitial cells show no noticeable change in structure.

Judging from the statements of Hewer (1914) and Allen (1918), there appears to be considerable variation in the age at which the various steps in the process of spermatogenesis occur in the albino rat. Hewer reported that there is no differentiation of primary spermatocytes from spermatogonia until the twenty-fifth day after birth. Allen found that his rats reached the pachytene stage at two weeks; while my material first shows this stage at three weeks. Hewer found that lumina first appear in the tubules at seven weeks. Allen demonstrated them in all rats fourteen days old. In my own rats fourteen days old I found no evidence of definite lumina, but they begin to appear at twenty-one days. Hewer stated that spermatozoa are not present in the lumina of the tubules until nine weeks after birth. Allen found spermatozoa in rats at the age of thirty-seven days, which corresponds closely with my observation at forty-three days.

CHANGES IN YOUNG RATS SUBJECTED TO ACUTE INANITION (GROUP II)

A comparison of the testes of the normal control (at four days) with those of the test animals of same age (but lesser body weight) in Table 1 shows but little apparent retardation in the growth in weight of the gonads of the latter (average weight in two controls, 0.0053 gm.; in three test rats, 0.0046 gm.). Although the test rats were kept on total inanition for forty-eight to fifty hours, the testes have evidently maintained nearly normal growth, although the body weight has decreased 21 to 25 per cent.

The remarkably persistent growth of the testes in the starved rats is especially evident upon comparison with the newborn of the same litter (Si 1.4). The starved rats have decreased in body weight until they, although four days old, are about 20 per cent below the normal newborn. The testes, however, show a large increase in weight (in spite of the total inanition). The change in weight from 0.0029 gm. to an average of 0.0046 gm. represents an increase of 59 per cent. This is in general agreement with the results of Stewart (1918), who found that in rats kept at maintenance (constant body weight) by underfeeding from birth to (average) sixteen days the testis apparently increased about 374 per cent in weight. The smaller increase in the testes of my starved rats is probably due to the greater severity and shorter duration of the inanition.

My measurements indicate that this increase of 59 per cent in the weight of the testes is due almost entirely to the increased number of tubules seen in a section. The size of the tubules has remained about the same. There has perhaps been some retardation of the normal growth in size of the tubules. The normal testis at four days shows an average tubular diameter of 41.7μ, while the average diameter of the tubules in Group II is only 38.4μ. This small difference, however, is of doubtful significance.

All three of the starved young rats (Si 1.1, Si 2.3, Si 2.6) show practically the same histological structure in the testis. The tubules are close together and more numerous than in the newborn, although there are relatively few in the center of the section. Cell differentiation has not progressed much beyond that found in the newborn. Each tubule presents the single layer of parietal cells. These cells are all alike and contain large nuclei, with very little chromatin material, surrounded by a narrow strip of clear cytoplasm. The central cells ('Ursamenzellen' of von Ebner) like those already described in the normal testis are also still present. There are very few mitotic figures either among the parietal cells or the central cells (Fig. 91). Sections (stained with iron-alum hematoxylin) of the testes of contrlos show many mitotic figures in each field (Figs. 84 and 85). This decrease in the number of karyokinetic figures is probably due to the condition of inanition. In general, the histologic picture shows that the testis has advanced to the stage when type A cells are beginning to appear. Thus the stage of differentiation is somewhat beyond that corresponding to the normal at similar body weight, but behind that corresponding to the age or actual testis weight. The increase in the (apparent) number of tubules evidently accounts for the increase in the size (weight) of the testis.

Swingle (1918) similarly found that total starvation inhibits the growth and metamorphosis of *Rana pipiens* larvæ. Spermatogenesis ceases and sex differentiation is prevented.

CHANGES IN RATS HELD AT MAINTENANCE BY UNDERFEEDING FROM THREE TO TEN WEEKS OF AGE (GROUP III)

In the five rats of this group held nearly at constant body weight by underfeeding from three to about ten weeks of age, the testes, though below normal weight for that age, have been retarded in their growth far less than has the body weight. Thus on comparing the average data for Group III (Table 1) with the normal control at three weeks (Si 6.0) it appears that the body weight has increased from 20.6 gm. to 26.9 gm., an increase of about 31 per cent; while the testes have increased from 0.0920 gm. to an average of 0.1955 gm., an increase of about 113 per cent. This would indicate a relative growth for the testis even greater than that (+34 per cent) found by Jackson[15] (1915) under similar conditions. Individual variations in the control or test rats probably account for the difference.

The size of the tubules in Group III has apparently increased from an average diameter of 99.7μ (normal at three weeks of age) to an average diameter of 110μ. This increase in diameter (though of doubtful significance) would indicate that the increase in the weight of the testes is due in part to the increase in the diameter of the tubules.

With the exception of one rat (S 11.65), which will be mentioned later, the testes in this group all present the same microscopic picture (Fig. 92). The tubules are placed close together. Lumina are just beginning to appear, although most of the tubules still show no central lumen. No spermatozoa or spermatids are present. There is no evidence to indicate that they had ever been developed and had undergone necrosis. A few secondary spermatocytes can be seen, but they are abnormal in structure.

Almost every primary spermatocyte also shows some degenerative changes. The cytoplasm becomes coarsely granular and contains clumps of basophilic staining material. Other cells show a fatty (?) degeneration or vacuolization of the cytoplasm (a positive statement cannot be made, as material stained for fat was not available). The nuclei degenerating by a process of karyorrhexis may give rise to the basophilic granules present in the cytoplasm of so many spermatocytes. The pycnotic nuclei are very abundant and, with progressive necrobiosis, appear gradually to lose their staining capacity, terminating in karyolysis. The cytoplasm also progressively loses its staining capacity and gradually disappears.

The spermatogonia, however, appear nearly normal. The Sertoli cells are increased in number, but show no structural changes. The tubules are filled with a structure resembling the 'degeneration reticulum' described by Kuntz (1919) in the testis after division of the nerves. This appears to me to be due largely to the Sertoli syncytium which becomes visible in direct ratio to the number of other cells which are being destroyed. Allen (1919) pointed out that in normal tubules the Sertoli syncytium is hard to see on account of the closely packed germ cells. As a result of experimental conditions, the syncytium is made more prominent by the removal of the germ cells which normally obscure it.

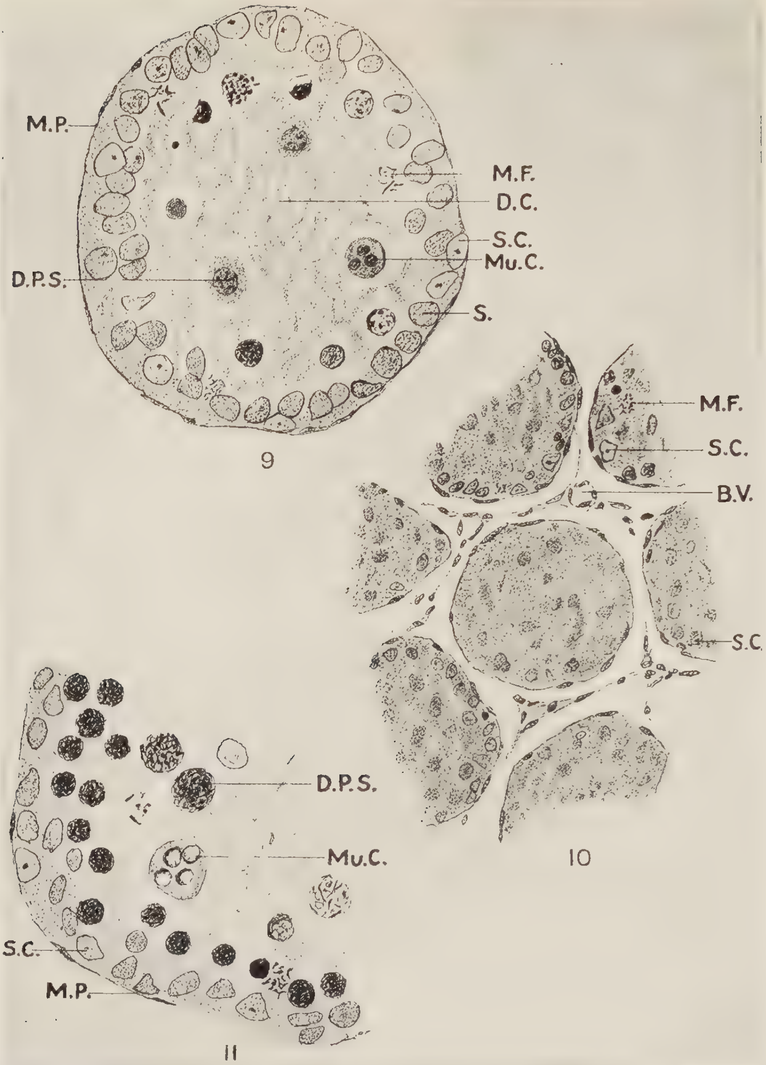

FIG. 92 (9).—Section of a tubule from a rat (S 7.32) held at constant body weight by underfeeding from three to ten weeks of age. Section 6μ thick; stained with hematoxylin and eosin. × 630. Degenerating primary spermatocytes, *D.P.S.*, showing the homogeneous, deeply acidophilic staining reaction of the cytoplasm. Note the persistence of mitotic figures, *M.F.;* the normal Sertoli cells, *S.C.*, and spermatogonia, *S.* A multinucleated cell, *Mu.C.*, typical of those appearing as a result of chronic inanition. Degenerating cytoplasm, *D.C.*; membrana propria, *M.P.*

FIG. 93 (10).—Section of a portion of the atrophic testis from a rat (S 11.65) subjected to chronic inanition from three to ten weeks of age. Section 10μ thick; stained with hematoxylin and eosin. × 127. The central tubule shows the extreme stage of degeneration (described in text), a complete nearly homogeneous mass of necrotic

There are present in all cases many multinucleated or giant-cells. These cells are situated in the center of the lumen, and each tubule usually presents one or two of them. Each cell may contain from two to four nuclei, all showing some degenerative changes. Multinucleated cells appear to be very characteristic of the degenerative process in the testis. To a certain extent, the degree of severity of the starvation can be measured by the size of these cells and the number of nuclei they contain. For example, absolute inanition for nine days (in the adult) produces giant-cells containing as high as twelve to fifteen nuclei, while in the slower chronic inanition in the present group, the number is reduced to three or four nuclei.

One other important fact, which is strikingly illustrated in these sections, is the remarkable persistence of mitotic figures in the spermatogonia and primary spermatocytes. In rats which have been kept at constant body weight by underfeeding for seven weeks, the number and structure of the mitotic figures is apparently normal as compared with control rats (from three to four weeks). This fact is in agreement with the observations by many investigators (mentioned later) who have reported the presence of mitotic figures after prolonged chronic inanition. This mitosis is doubtless correlated with the persistent growth of the testis in the underfed young rats under these conditions, the new cells formed being in excess of those destroyed by degeneration.

My study of this group of albino rats kept at maintenance by underfeeding from three to ten weeks leads to the following conclusions: First, the chronic inanition prevents the testis from reaching the stage of spermatogenesis normal for the corresponding age. Second, in spite of the persistent mitosis and increased size of the testis, the process of spermatogenesis remains at the stage where spermatocytes are produced, corresponding to the normal stage at the age of three or four weeks. The growth capacity of the testis under these conditions of subnormal nutrition is apparently sufficient only to produce primary spermatocytes from the spermatogonia.

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tissue. The surrounding tubules show various stages of degeneration. Note the mitotic figures, *M.F.*, in the tubule to the right and the apparently normal Sertoli cells, *S.C.* A slight hyperplasia of the interstitial cells, *I.C.*, appears. Blood-vessel, *B.V.*

Fig. 94 (11).—Portion of a tubule from the testis of a rat (St 44.4) stunted by underfeeding from three weeks to 428 days of age. Section 10μ thick; stained with hematoxylin and eosin. × 630. Note the degenerating primary spermatocytes, *D.P.S.*; the multinucleated cell, *Mu.C.*, in the lumen. Sertoli cells, *S.C.*, and spermatogonia, *S.*, are apparently normal. Membrana propria, *M.P.*

Third, the spermatocytes degenerate and are absorbed, though not so rapidly as they are formed. The excess of production over destruction partly accounts for the continued growth in weight of the testis. Fourth, the interstitial tissue is apparently unchanged and resembles in quantity and structure the tissue present in a normal rat at the age of three or four weeks.

In one rat (S 11.65 Fig. 93) in this group, the testis shows such remarkable changes that it seems advisable to describe it separately. This was the left testis (indicated by (L) in Table 1), which was markedly atrophic, weighing only 0.0496 gm. All the tubules show degenerative processes. Many contain no cells whatever. The lumina are filled with the characteristic 'degeneration reticulum,' and some have large vacuoles in their centers. Pycnosis, karyorrhexis, and karyolysis are prevalent.

A few of the seminiferous tubules in this case show a type of degeneration which differs entirely from any other thus far described. All the nuclei in every cell in the tubule gradually and almost uniformly lose their basophilic staining capacity and become acidophilic, taking the red counterstains. At the same time the cytoplasm of all the cells fuses together and becomes homogeneous in appearance. So that the entire cytoplasm in the tubules finally becomes one single mass, resembling very closely the homogeneous mass of necrotic tissue seen in an infarct. This mass apparently undergoes a process of autolysis, and vacuoles later replace the cytoplasmic substance. This process continues until finally the structure disintegrates and the position of the tubule is indicated by only the membrana propria. In spite of this necrosis in the tubules, the intertubular tissue shows no marked degenerative changes. However, a very irregularly distributed moderate hyperplasia of the interstitial cells is apparent (Fig. 97, *D*). While not the typical picture produced by the chronic inanition in Group III, this condition evidently corresponds to the advanced degenerative process in an extreme case.

CHANGES IN YOUNG RATS RETARDED BY UNDERFEEDING FOR LONG PERIODS BEGINNING AT THREE WEEKS OF AGE (GROUP IV)

In the three rats underfed from three weeks to two hundred twenty-three to four hundred twenty-eight days of age (Table 1) the body has approximately doubled in weight, whereas normally it should have increased to about twelve times the initial weight. The testes are likewise of course far below norm for the corresponding age, though apparently considerably above the norm for the younger rats of similar body weight (rats Si 10 and Si 11; also Donaldson's Wistar norm). Stewart (1918), however, concluded that in rats underfed beginning at three weeks of age so as to reach only about 50 gm. in body weight at four hundred and twelve days of age the testes average 42 per cent below normal (for corresponding body weight). It is evident that the changes in the weight of the testis are extremely variable, so it is unsafe to draw general conclusions from only a few cases.

Judging from the size of the tubules in normal testes of similar weight, the tubules in Group IV should average above 200μ in diameter. As shown in Table 1, however, in three of the four cases the tubules appear subnormal (90 to 120μ) in diameter.

Microscopic sections (stained with hematoxylin and eosin) of the testis show that the size of the tubules in these rats long underfed has considerably decreased. The number of tubules has also decreased and they have become widely separated (Fig. 94), due in part to the accumulation of fluid in the interstitial spaces (edematous infiltration). No mature spermatozoa or spermatids appear, although they are present in normal rats of corresponding body or testis weight. Spermatogenesis here (as in Group III) has apparently not passed the primary spermatocyte stage. Most of the tubules contain three to four layers of cells, composed of spermatocytes and spermatogonia. The former show the most profound changes. Some appear as shadows without any nucleus or cytoplasm. Others have pycnotic nuclei and a homogeneous cytoplasm. Multinucleated giant-cells are present and the nuclei in these cells show pycnotic changes. Many spermatogonia and all the Sertoli cells appear normal. Mitotic figures are still present. Apparently some vascular changes have taken place. There is a slight sclerosis in the walls of the blood-vessels and also (apparently) a reduced blood-supply to the tubules. There is not any noticeable increase in the quantity of interstitial tissue (proper) (Fig. 97, *E*) or any appreciable change in the structure of the interstitial cells, but the quantity of interstitial fluid has enormously increased.

Since all three rats (St 44.1, St 44.4 and St 44.7) show the same histologic structure, the question of individual variation may be excluded. So that it appears that the 'growth tendency' so strongly manifested in the testis during inanition in young animals is confined to the formation of the earlier cells in the spermatogenetic cycle; that is, the process can go only to the spermatocyte stage. This is probably what happened in the case of the rats in Group III, as before mentioned.

In one rat (M 29.109) inanition was started at ten weeks of age after the testis had presumably reached the stage when mature spermatozoa are produced. Even though kept at maintenance (constant body weight) by extreme underfeeding for two hundred forty-four days, this testis shows the following histologic structure. Most of the tubules are normal in structure and size and show well-developed spermatozoa. However, many lumina are filled with a débris made up almost entirely of heads and tails of spermatozoa. A few tubules show a slight desquamation process, but this is not distributed evenly among the tubules and is probably of no importance. Aside from this, the structure of the testis is apparently normal. Mitotic figures are present and all the various stages of spermatogenesis can be followed out. The conditions in this case emphasize the importance of the age factor. It indicates that if the testis has reached sexual maturity before experimental inanition, the effect upon spermatogenesis is much less marked than in cases where the underfeeding is begun at an earlier period, although the further growth of the testis (in weight) may be hindered. No final conclusions can be drawn from this one rat, however, although the results are in agreement with the conclusions of Jackson and Stewart (1920) as to the importance of the age at which the inanition begins.

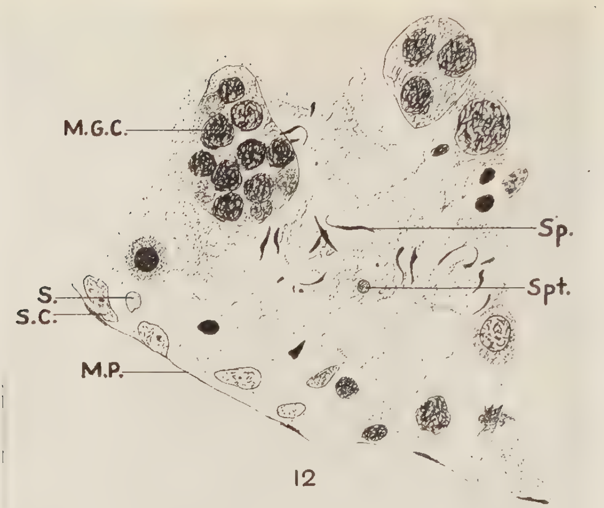
CHANGES IN ADULT RATS AFTER ACUTE INANITION (GROUP V)

As shown in Table I (Group V), adult rats were subjected to acute inanition for periods varying from nine to twelve days. The loss in body weight varies from 30 to 47 per cent. The testes also apparently lose a great deal in weight, but the exact amount can of course be only roughly estimated. The test rats at the beginning of the experiment varied in body weight from 216 gm. to 328 gm. According to the Wistar norm tables compiled by Donaldson (1915), these body weights call for from 2.5 gm. to 2.8 gm. of testis. A comparison with the figures in Table 1 shows that at necropsy the testes in weight varied from 1.468 gm. to 2.43 gm., indicating considerable loss in weight. The average diameter of the tubules has correspondingly decreased from over 300μ to an average of 221.5μ. Jackson[14] (1915) found that the loss in weight of the testis of adult rats during acute inanition is nearly proportional to that of the whole body. This agrees in general with the results obtained by Falck (1854), Voit (1866), Manassein (1868), and Gerhartz (1909). An atrophy of the testis relatively much greater than the decrease in body weight during inanition was noted in birds by Grandis (1889), and (during vitamine deficiency) by McCarrison (1919) and Dutcher (1920). A similar result in rats fed by McCollum on a lipoid-free diet (also deficient in vitamines) was noted by Hatai (1915).

In one rat (Si 9) which was held for eleven days without food or water, the testis had shrunken away from the tunica albuginea and had decreased considerably in size. This was, however, not apparent upon removing the organ at necropsy, because the intervening space was filled with a fluid, which kept the tunic distended and gave it a normal rounded appearance. This phenomenon has likewise been noted by Allen (1919) in his study of rats subjected to a diet deficient in the water-soluble vitamines.

At first glance, the sections of the testes in this group appear perfectly normal in structure. The majority of the tubules are apparently normal in shape and show no signs of degeneration, as was likewise noted by Simonowitsch (1896). Spermatogenesis appears to be going on as usual. Spermatozoa are abundant and show no alteration in structure. There is no apparent change in the amount or structure of the interstitial tissue.

However, more careful study shows that in each section a few tubules have suffered as a result of the inanition. These tubules, though few in number and placed in immediate relationship with perfectly normal tubules, may show very marked and very severe changes (Figs. 95 and 96). The spermatozoa are irregular in structure and show extreme degenerative processes. The spermatids may present a picture which strongly suggests a true synizesis. This peculiar clumping of the chromatin toward the periphery and toward one side of the nucleus has been described by Monterosso (1912) as a form of degeneration. But I have observed this same structure in almost every one of my control rats, and believe that we are dealing here rather with a rearrangement of the chromatin material in the normal cytomorphosis of the cell.



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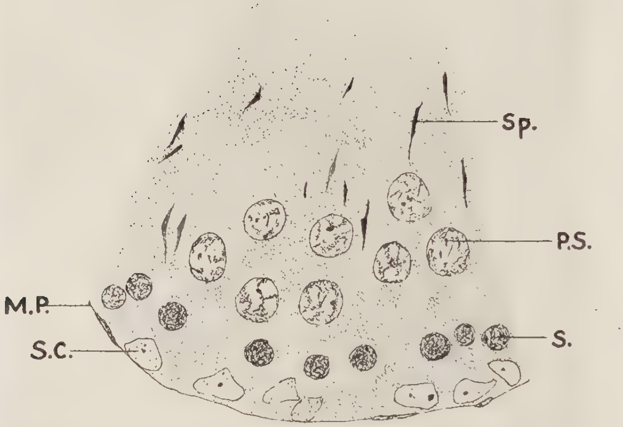

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Fig. 95 (12).—Oblique section of a testis from an adult rat (S 25) subjected to acute inanition for nine days. Section 10μ thick; stained with hematoxylin and eosin. × 630. Multinucleated giant-cells, *M.G.C.*, occupy the center of the tubule. Débris composed of degenerating cells of various kinds fills the tubule. Spermatozoa, *Sp.*; spermatids, *Spt.*; spermatogonia, *S.*; membrana propria, *M.P.* The Sertoli cells, *S.C.*, still occupy their normal position, but show atrophic and degenerative changes.

Fig. 96 (13).—Portion of transverse section of the testis from a rat (S 12.52) underfed from three to ten weeks of age and then refed for thirty-seven days. Section 7μ thick; stained with hematoxylin and eosin. × 630. Note the large number of normal primary spermatocytes, *P.S.*, and spermatozoa, *Sp.* Spermatogonia, *S.*, showing mitotic figures, are abundant. Sertoli cell, *S.C.*; membrana propria, *M.P.*

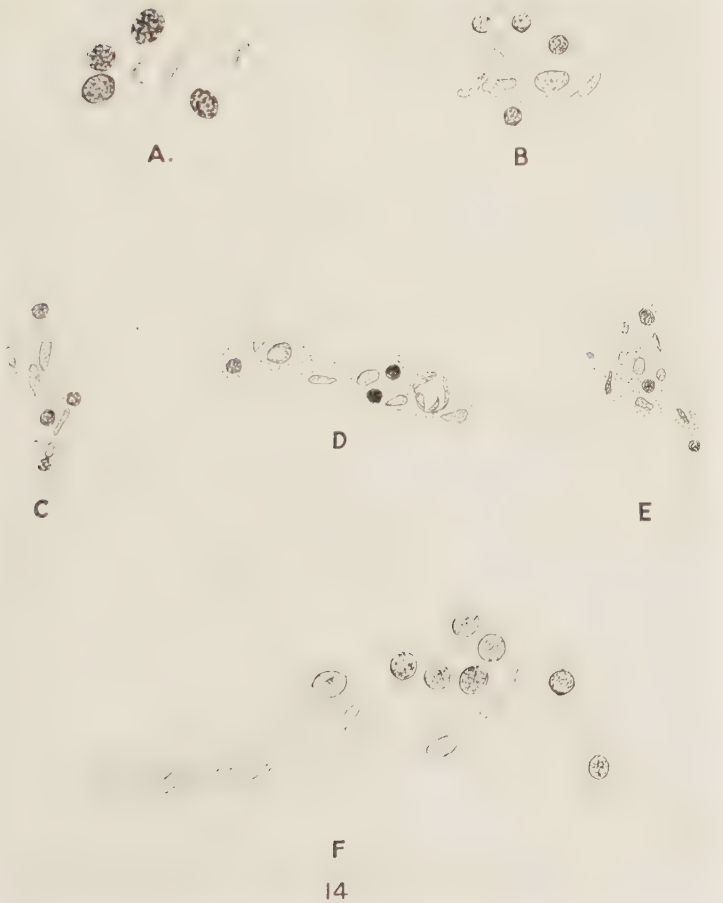

Fig. 97 (14).—A to F represent various stages in the interstitial (mesenchymal) cells of the testis during normal development, inanition, and refeeding. All magnified × 630. *A*, normal newborn (Si 1.4). *B*, normal adult (S 14). *C*, underfeeding, three to ten weeks of age (S 7.32). *D*, extreme atrophy in underfeeding from three to ten weeks of age (S 11.65). *E*, underfeeding from three weeks to 428 days of age (St. 44.4). *F*, refed thirty-seven days after underfeeding from three to ten weeks of age (S 12.52).

The secondary and primary spermatocytes show marked necrobiotic changes. Even the spermatogonia are involved and reveal pycnotic and karyolytic changes in the nuclei. The Sertoli cells are apparently the only ones not severely injured.

Depending on the stage of degeneration, large numbers of multinucleated giant-cells are present in the tubules. These cells each contain from four or five nuclei up to as many as twelve or fifteen nuclei. Some tubules are so atrophic and degenerated that only the membrana propria remains, with a few necrotic giant-cells in the lumina. These giant-cells were carefully studied with special reference to their origin. Apparently they are derived from primary spermatocytes, which fuse together in groups during their desquamation. These cells will be referred to again at a later period.

Desquamation of the epithelial cells in these degenerating tubules is very common and apparently initiates the process of degeneration. This process appears to start with the secondary spermatocytes, but as the sloughing process continues the primary spermatocytes and even the spermatogonia are detached into the degenerating mass in the lumen of the tubule. Degeneration takes place in every case after desquamation has occurred. This degeneration apparently is also always in inverse order to that of spermatogenesis. The spermatozoa are the first to disappear, then the spermatids, followed by the spermatocytes and spermatogonia. The Sertoli cells are the most resistant. This agrees with the results obtained by Monterosso (in starved rats), Bouin and Garnier (1900) (in alcoholized rats), and Regaud and Tournade (1903) (after ligation of the spermatic cord). Allen (1919) states that (in degeneration due to vitamine deficiency) "the spermatocytes seem to be the first affected, the spermatids next, and the spermatogonia last."

It therefore appears that acute inanition notably affects but comparatively few tubules in the testis, and that the other tubules retain their normal structure, but all the tubules suffer a loss in size. In spite of a loss of about one-third in the weight of the testis, spermatogenesis apparently continues normally in most of the tubules. But the few tubules which for some unexplainable reason are less resistant show atrophic and necrotic changes which are as marked as any found in chronic inanition.

Likewise, atrophic and degenerative changes in the seminiferous epithelium during inanition have been described by Grandis (1889) in pigeons, Pernice and Scagliosi (1895) in chickens, Simonowitsch (1896) in rabbits and guinea pigs, Loisel (1901) in the dog, Monterosso (1912) in rat and mouse, and Poiarkov (1913) in the dog. Similar changes have been described as a result of vitamine deficiency by McCarrison (1919) in pigeons and by Allen (1919) in rats.

The extent of the degenerative changes naturally varies in general with the severity of the inanition. In the adult rabbit, Traina (1904) found that spermatogenesis ceases when the loss in body weight reaches about 30 per cent.

There is also a variation according to species, season, etc. At certain periods the testis during inanition may even continue to develop at the expense of the remainder of the body in the salmon (Miescher, 1897) and frog (Nussbaum, 1906).

CHANGES IN RATS REFED AFTER UNDERFEEDING BEGINNING AT THREE OF AGE AND EXTENDING FOR VARIOUS PERIODS (GROUP VI) WEEKS

In one rat (St 12.53) refed for three and one-half days (Table 1), the refeeding period was too short to produce any definite results. There is apparently already some increase in the total body weight, but very little, if any, in the testis. Sections show no definite change from the appearance of the testes in Group IV. The primary spermatocytes still show necrotic changes and there is no advance in the stage of spermatogenesis. The average diameter of the tubules (98.7μ) is slightly below that in rat S 7.32 ,with similar testis weight.

In another rat (St 10.26), refed for fourteen days after maintenance by underfeeding from twenty-one to seventy-two days, many improvements have taken place. The body weight has increased from around 30 gm. to 86.3 gm., but there is no great increase in the weight of the testes. The reason for this becomes more evident upon histological study. Sections (stained with iron hematoxylin) show no increase in the number and but slight increase in the diameter of the tubules, compared with those of Group III. But all the débris has been removed and no degenerating cells are to be seen (Fig. 96). No secondary spermatocytes are present. The interstitial cells and their nuclei appear normal (but increased in size). They are, however, definitely increased in number above normal. They are evenly distributed throughout the testis, in this way differing from the condition found by Allen (1919) in the rats of Osborne and Mendel subjected to a diet deficient in the water-soluble vitamines. There are numerous mitotic figures among the spermatocytes and spermatogonia, showing all the stages of the karyokinetic cycle. The blood-vessels are distended with blood. It would appear that all the energy in the testis has been utilized to 'clean up' the waste material and to prepare for a further advance. This may account to some extent for the lack of increase in the weight of the testis.

In the rat (S 12.52) which was refed for thirty-seven days, the weight of the testis has greatly increased and histological study shows that spermatogenesis is going on normally. The tubules are normal in structure and contain many mature spermatozoa. The average diameter of the tubules has, however, increased to 222.7μ accounting for the increase in weight. The only difference to be found (as compared with normal control testes) is an increase in the amount of interstitial tissue (Fig. 97, *F*).

We must distinguish between interstitial tissue and interstitial cells. The former term applies to all tissues outside of the tubules proper; the latter (interstitial cells) refers only to the specific cells playing a part in the internal secretion of the testes. In reality, there is not so much a general hypertrophy of the interstitial tissue, but rather a hyperplasia of the interstitial cells proper. There is a marked increase in the number of these cells and a slight increase in their size. They assume a more or less cord-like arrangement. The nuclei of the cells are spherical and rather vesicular, although a few clumps of chromatin are always present close to the periphery. A light granular cytoplasm surrounds the nuclei. After the very young stages (one to seven days), mitosis among these cells has never been observed. One possible explanation which may be offered is that mitosis in these cells takes place very rapidly, so that, although cell division occurs, it is rarely found in the sections.

The fourth rat in this group (S 33.118), refed for two hundred and six days, has completely recovered from the effects of the underfeeding and presents a perfectly normal adult histologic structure. The diameter of the tubules shows an increase of 291.1μ. Even the interstitial tissue and cells appear normal in quantity and structure.

These results are in accord with the work of Stewart (1915), who found that in rats refed after underfeeding from three to twelve weeks of age, the testes remain somewhat below normal weight for a few weeks, but regain normal weight before the adult stage is reached. In later experiments (Stewart, 1918), in which the underfeeding was prolonged, the testis became markedly subnormal in weight (as found by Jackson,[15] 1915). Jackson and Stewart (1919) reported that the testis, which increases in relative weight in young rats during underfeeding, remains somewhat above normal weight during refeeding to a body weight 25 gm. to 50 gm., but is subnormal in those refed to 75 gm. body weight. Finally, Jackson and Stewart (1920) found that when the underfed rats are fully refed to maximum body weight, the testes are definitely above normal for the corresponding body weight. A restoration of the testis to normal structure and function upon refeeding after inanition has likewise been noted by Simonowitsch (1896) in rabbits and guinea-pigs, and by Loisel (1901) and Poiarkov (1913) in dogs.

DISCUSSION

Origin and significance of polynucleated giant cells.—It has been claimed by some authors that giant-cells may occur normally in the testis. I have never seen either a polynucleated or a giant-cell in a normal seminiferous tubule. Monterosso (1912) found that these cells are very rare in normal tubules, but occur more frequently during early inanition. He found that their number increases with the length of inanition, and that as many as fifteen nuclei might be seen in a single cell. He believes that they are formed by a fusion of the neighboring cells.

On the other hand, Bouin and Garnier (1900) believe that these cells are formed by an abnormal mitosis of the nuclei within the cell. Allen (1919) noticed these cells during the early stages of degeneration, but offered no explanation as to their origin.

My studies lead me to believe that the multinucleated cell is formed by a fusion of primary spermatocyte cells when they begin to degenerate. As a rule, these cells show marked nuclear and cytoplasmic degenerative changes later than those cells which break off independently and do not fuse with other cells. This suggests that fusion of cells may be a sort of protective measure from the effects of the inanition. de Bruyne (1899), however, claims that these polynuclear cells are precursors of degeneration. No mitotic figures have ever been observed in any polynucleated giant-cell.

2. *Mitosis during inanition.*—As to the occurrence of mitosis during inanition, my own observations agree in general with those of Morpurgo, (1888, 1889), Grandis (1889), Traina (1904), and others.

Traina, for instance, found that mitotic figures persist after a loss in body weight of 30 per cent to 35 per cent. On the other hand, Pernice and Scagliosi (1895), in young chickens on water inanition, and Morgulis, Howe, and Hawk (1915), in fasting dogs, reported an absence of mitosis in the testis. In my adult rats subjected to acute inanition (S 25, S 26, S 27), with loss in body weight of 30 per cent, 35 per cent and 39 per cent, mitotic figures are still present in large numbers. Another rat, (Si 9), with loss in body weight of 47 per cent, still shows numerous mitotic figures. They are present even in tubules showing extreme degenerative changes. In young rats underfed from the age three to ten weeks, mitosis is apparently unaffected. Even in those animals in which the underfeeding was continued to four hundred days or more, the mitotic figures can be seen in many of the tubules. It would therefore appear justifiable to conclude that it is impossible by inanition to suppress mitosis entirely in the epithelium of the seminiferous tubule. The mitoses, however, may be decreased in number, as found in the rats two days old subjected to acute inanition.

The presence or absence of amitosis in the testis has long been a disputed question. Monterosso (1912) found amitosis present among degenerating spermatocytes and spermatogonia. Allen (1918, 1919) believes that amitosis does not occur. I have likewise never seen a definite case of amitosis in any of my sections.

Interstitial tissue during inanition.—Some investigators mention the increased quantity of interstitial tissue, which is occasioned by any degeneration or atrophy of the seminiferous epithelium. Cordes (1898) found an increase in interstitial tissue in cases of chronic disease with cachexia. Kyrle (1910) and Voss (1913) pointed out that in diseased conditions and in underdeveloped testes, the tubules are far apart and the interstitial tissue surpasses the tubules in amount. Allen (1919) also found an increase in the quantity of interstitial tissue in rats fed upon a diet deficient in water-soluble vitamines.

In my own series of albino rats, there appears in no case any demonstrable increase in interstitial tissue during either acute or chronic inanition. However, in those rats which were refed after various periods of underfeeding (Group VI), there is a gradual increase in the relative amount of interstitial tissue (interstitial cells) until the gland regains its normal size and structure. Thereafter, the interstitial tissue apparently decreases in amount until it reaches the normal proportion. That is, the interstitial cells appear relatively increased in number only during the regenerative period.

Measurements of the nuclei of interstitial cells indicate that there is a sharp decrease in the average diameter of the nucleus from 7.1μ at birth to 4.7μ at three weeks of age. From the three-weeks stage there is very little change in the size of the nucleus. Comparison with the test groups indicates that the size of the nucleus of the interstitial cells is not affected to any marked degree by the inanition tests. In Group III, two of the three specimens measured show a decreased average diameter of the nucleus (in underfeeding from five to ten weeks of age); and in Group VI, it would appear that refeeding causes some increase in the size of the nucleus, in addition to the numerical increase already noted. There is considerable individual variation, however, and the number of observations is insufficient to warrant final conclusions.

SUMMARY

The results of the present investigation may be summarized as follows:

1. In the normal testis of the albino rat during the first postnatal week the (solid) seminiferous tubules consist of a single layer of parietal cells ('Sertoli cells' of von Ebner) and a few central cells ('Ursamenzellen' of von Ebner). After the first week, the normal postnatal development of the testis and the process of spermatogenesis proceed essentially as described by Allen (1918).

2. In rats two days old starved for forty-eight to fifty hours, the testis increases markedly in weight, but mitoses are reduced in number and the normal process of histological differentiation is arrested. The seminiferous tubules remain nearly normal in diameter.

3. During underfeeding for various periods beginning in rats three weeks old, mitosis continues in the cells of the seminiferous tubules, but the process of spermatogenesis is arrested at the primary spermatocyte stage, which persists even in rats over four hundred days old. The spermatocytes degenerate and are resorbed, but if the number formed exceeds those destroyed, the testis may increase in weight. Multinucleated giant-cells are formed during the process of degeneration. The spermatogonia and Sertoli cells usually persist unaffected, except in very extreme cases, where a complete degeneration and disintegration of the seminiferous epithelium may occur. If the under-

feeding begins after sexual maturity, the seminiferous tissue is much more resistant and normal spermatogenesis may persist for a long time. The seminiferous tubules may increase slightly in diameter in the shorter tests, but usually appear subnormal in size in the longer experiments.

4. Acute inanition in adult rats, with 30 per cent to 47 per cent loss in body weight, produces degenerative changes in a few, irregularly scattered, tubules. All the other tubules show apparently normal structure and spermatogenesis, although there is a general decrease in their size. The degenerative changes are initiated by a desquamation of the epithelial cells into the lumen of the seminiferous tubule, followed by pycnosis and karyolysis. The process involves first the spermatids and spermatozoa, then the secondary and primary spermatocytes, and finally the spermatogonia. The Sertoli cells are the most resistant. During the degenerative process, multinucleated giant-cells arise, apparently by fusion of the degenerating spermatocytes.

5. During inanition, mitosis is very persistent in the seminiferous epithelium, both in young and adult rats. It may occur even in tubules where nearly all the cells are more or less degenerated. Amitosis was not observed. A condition resembling synizesis was frequently observed in the spermatids in both controls and test rats.

6. Refeeding after prolonged inanition (beginning in rats at three weeks of age and extending to twelve to twenty weeks) results in a rapid improvement in the structure of the testis, although it may lag behind in weight for a while during the preliminary stages of reconstruction. Spermatogenesis returns to normal in a short time, the tubules gradually increase to normal diameter, and spermatozoa appeared in thirty-seven days.

7. There is a definite hypertrophy of the interstitial tissue and an increase in the number of interstitial cells of the testis during the regenerative period on refeeding after inanition (in growing rats). No hypertrophy of the interstitial tissue was found accompanying atrophy of the seminiferous epithelium during inanition in either young or adult rats. The structure of the interstitial tissue and the size of the nuclei apparently remain nearly normal during acute and chronic inanition, except in extreme cases, where degenerative changes in the cells may occur.

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STUDIES ON THE OVARY OF THE SPERMOPHILE (SPERMOPHILUS CITELLUS TRIDECEMLINEATUS) WITH SPECIAL REFERENCE TO THE CORPUS LUTEUM*

DELLA G. DRIPS

In the summer of 1914, while the writer was studying microscopic sections of the various tissues and organs of the spermophile, the relatively immense size of the ovaries, compared with those observed the previous spring, strikingly presented itself. On further comparison it was very evident that this great increase in size had been brought about by a growth in the corpora lutea only. One ovary contained eleven of these bodies; there remained only a framework of ovarian stroma, with a few atretic follicles.

From observations that had been going on it was known that these spermophiles had given birth to young about a month before. According to most writers, degeneration of the luteal cells begins not later than birth. Here were what looked like actively secreting cells a month after birth. Thereupon it was decided to try out some differential stains on these luteal cells at every stage in their life history, and to study the complete ovarian cycle in the spermophile with a view of gaining some accurate information of the origin, development, life history, and function of the corpora lutea of the ovary.

In the spring of 1915 numbers of spermophiles were captured. But not having realized how very soon the animals become impregnated after coming out of hibernation, no strenuous efforts were made to obtain them until they were quite numerous in the fields, and consequently they were found to be either in advanced stages of pregnancy or lactating. However, all the animals that could be obtained were used for a study of the ovarian cycle through the summer and fall, until hibernation began.

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Several animals were sacrificed each week. They were killed quickly with ether and bleeding. The ovaries were immediately placed in one of several fixatives, 10 per cent formalin, Zenker's fluid with acetic acid, Bensley's formalin-Zenker, and Bensley's acetic acid bichromate. Many stains were experimented with. After considerable study of the fixed and stained sections, it was decided that for the problem in hand two fixatives seemed best, Bensley's formalin-Zenker and Bensley's acetic osmic bichromate, the former particularly for the nuclear structures and the latter for the elements in the protoplasm. In all the work of the past spring (1916) one ovary of each animal sacrificed was routinely placed in formalin-Zenker and the other in acetic osmic bichromate.

Of the sections fixed in Zenker, the best results were obtained with a modified Weigert stain (copper-chrome-hematoxylin), Ehrlich's hematoxylin and eosin, Mallory's connective-tissue stain, and Bensley's acid fuchsin and methyl-green. A few sections of each series were prepared with these stains.

Of the sections fixed in acetic osmic bichromate, one of each series was stained with the Weigert stain, and several with the acid fuchsin and methyl green of Bensley. Complete paraffin serial sections were made of all the ovaries studied.

The spermophiles went into hibernation about the middle of October, although many of them became partially torpid earlier than this. The next spring it was determined to get them early enough. The frost was not out of the ground until about April 15. With a great deal of difficulty the females were obtained while in rut, and every day through the period of pregnancy, which was found to be about twenty-eight days. Two or more were sacrificed each day.

The ovarian cycle was now completed. Ovaries were at hand for every week of the year except during the hibernation period, when only a sufficient number of animals was sacrificed to make sure that changes were not taking place in these organs. For the period of pregnancy, a time which is especially related to ovarian activity, there were ovaries for even fractions of a day.

SUMMARY AND CONCLUSIONS

The results obtained from the histologic and experimental investigations carried on may be summarized as follows:

1. In the spermophiles, ovulation occurs only once a year, during

the rutting season in the early spring. Ovulation is dependent on the stimulus of coitus, for no corpora lutea were found in the ovaries of animals which were kept from the males.

2. The corpora lutea cannot be responsible for the phenomenon of rut, for they are not present in the ovaries at this time.

3. The corpora lutea develop and pass through their normal cycle after ovulation, whether fertilization follows or not.

4. While the corpora lutea are present in the ovaries, especially during the two months following parturition, the process of developing and ripening the follicles is at a standstill.

5. If the uterus is removed after conception, the corpora lutea do not begin to degenerate, but pass through their normal cycle. No effects are noted in the ovaries.

6. Removal of the uterus at any time does not produce noticeable effects on the ovaries even after a year's time.

7. Double ovariectomy performed at any time during the period of pregnancy interrupts gestation. If the operation is performed after a little more than the first half of pregnancy, the placentas with the fetuses simply degenerate. The involution of the uterus in these cases is very abnormal. If both ovaries are removed late in pregnancy, the animal aborts and the uterus undergoes a much more normal involution. The removal of only one ovary does not interrupt the pregnancy.

8. Double ovariectomy at any time prevents the recurrence of the cyclic changes in the uterus and produces an atrophy of the organ scarcely noticeable within a year.

9. The corpora lutea apparently do not influence the development of the mammary gland. When the uterus was removed very soon after conception, before any signs of pregnancy could be noted grossly in the uterus, and before any development of the mammary glands could be noted grossly, the developing corpora lutea in the ovaries produced no development in the mammary glands. This would seem to substantiate the work of Lane-Claypon and Starling, who attribute to the fertilized egg the stimulus for the development of the mammary glands.

10. The corpus luteum of the spermophiles derives its elements from the follicle just as Sobotta states occurs in the mouse. The luteal cells are the transformed granulosa cells of the follicle. The connective-tissue and vascular network are derived from the cells of

the internal theca, which spends itself entirely in their formation. The capsule of connective tissue surrounding the luteal structure is the same external theca which surrounds the follicle. The microscopic pictures of the corpora lutea in the succeeding stages of their development correspond also to Sobotta's descriptions. It may be well to emphasize the complexity of the vascular network throughout the luteal structure which, when it is completed, brings every luteal cell in intimate contact with the blood-stream.

11. The life cycle of the corpus luteum is made up of three distinct phases. First, the phase characterized by the presence of great numbers of red granules in the protoplasm of the luteal cells. This phase embraces a period dating from the bursting of the follicle and covering the entire period of pregnancy. From a point of time very shortly after the bursting, the protoplasm of the luteal cells shows these red granules, which become more and more abundant until they seem to reach a crisis of abundance when the organization of the luteal structure is about perfected, which is not until the placental swellings have reached a length of about 8.5 cm. From this time on the granules seem very gradually to decrease in number in the cells until parturition, when there is a sudden considerable reduction in their number. Some are found in the cells, howeveı, even as late as the fourth week after parturition. Second, the phase characterized by the presence of many lipoid droplets in the protoplasm of the luteal cells. This phase begins some time before parturition and lasts for about six weeks afterward. About the fourteenth day of pregnancy, when the placental swellings in the uterus measure 1.5 cm. to 2 cm. in length, the lipoid droplets usually begin to make their appearance at the periphery of the luteal cells, next to the capsule of the corpus luteum. They increase in number until, at the time of parturition, they are quite noticeable in the cells, being found scattered all through the protoplasm among the red granules. After parturition there seems to be a more rapid increase in the number of lipoid droplets, which coincides with the sudden decrease in the number of red granules previously noted. With this increase in lipoid content the cells, which, from the beginning, have been growing constantly larger, seem to begin to hypertrophy more rapidly. The luteal cells are largest and contain the greatest amount of lipoid about six weeks after parturition. In two more weeks practically all the lipoid has disappeared from the cells and they are beginning to show evidences of degeneration. Third,

the phase of regression. This period begins about eight weeks after parturition and lasts for four weeks. By the last of August the corpora lutea have disappeared from the ovaries. This phase is characterized by a fatty degeneration of the luteal cells, by increased vascularization, and by a connective-tissue invasion. From these results the following conclusions were drawn as to the functions of the corpora lutea in the ovaries of spermophiles:

The corpora lutea fix the periods of estrous by preventing the development and the ripening of the follicles until the time for the next rutting season is at hand.

The corpus luteum is a gland with two internal secretions, both of which have specific effects on the uterus, one bringing about the changes incident to pregnancy and the other effecting the normal involution of the organ. The first internal secretion is represented in the luteal cells during the period of pregnancy by granules which are very similar in their location and staining reactions to the granules in the A cells of the islands of Langerhans, the glands of internal secretion of the pancreas, described by Bensley. The granules of the luteal cells, however, are much larger than those of the A cells, being very easily seen with high powers of the microscope. No mitochondrial granules or filaments could be observed, perhaps because of the abundance of the granulations in the protoplasm. These luteal cell granules are very much like other secretion granules described by various writers as occurring in the secreting serous cells of several glands of the body.

The majority of writers have agreed that there is no fatty product demonstrable in the corpus luteum of several species of animals and man in the very early stages. They all seem to have been of the same opinion that the activity of the ovarian gland of internal secretion begins with the appearance of the lipoid droplets in the cells. These lipoid droplets were considered by them to be the evidence of the secretory activity of the corpus luteum. Its period of activity would then begin when the droplets begin to appear in the cells, which time varies with different species, but in all seems to be about the time of the fixation of the blastocyte. This activity lasts, they consider, for varying periods in different species. In the rabbit, Cohn, Fraenkel, and Niskoubina consider that it lasts for nine or ten days; regression sets in about the fifteenth day. Van der Stricht says that in the bat the lipoid droplets are in much greater abundance during the second half of the period of pregnancy and that regressive changes do not begin until the period of pregnancy is over. Miller says there is no neutral fat in the human corpus luteum until regression sets in at birth. Because the first-mentioned group of men found that double ovariectomy did not cause abortion in rabbits after the fifteenth day, and did so earlier than this, they considered this lipoid secretion related to changes in the uterus occurring between the fourth and fifteenth days after coitus, or between the time of the fixation of the blastocyte and the middle of the period of pregnancy.

Van der Stricht seems to have been the first to conceive of the presence of a secretion in the luteal cells prior to the appearance of the lipoid droplets which co-exists with them for some time after their appearance. He judges of the presence of this secretion in the cells from its presence in the near-by intercellular spaces and lymphatics. The latter, according to Van der Stricht, are the avenues of excretion of both the serous and the lipoid secretions.

In spermophiles, the lipoid product does not begin to appear in the luteal cells until the period of pregnancy is half over and is not very abundant until after birth. As far as these animals are concerned, then, the lipoid product is not the active substance of the corpus luteum, which has specific effects on the uterus during pregnancy. This active substance is rather a secretion represented in the cells by the secretory granules previously noted, which are of a very different nature from the lipoid droplets.

The second internal secretion which is represented in the luteal cells by lipoid droplets and which has been considered the secretion which is responsible for the changes in the uterus incident to pregnancy, must be considered, as far as the spermophiles are concerned, at least, as having another function. There seems to be some relationship in these animals between the period of greatest abundance of the lipoid product in the cells and the period of regression and atrophy in the uterus. The uterus of the spermophile atrophies very slowly, much more so than in animals that bear several litters of young every year. The atrophy is not completed until six or seven weeks after parturition, about the time when the lipoid product reaches its crisis of abundance in the cells and begins to disappear. Another result which substantiates the theory that the lipoid secretion brings about the normal involution of the uterus is the very abnormal, even pathologic, process which goes on in the uterus following the removal of both ovaries during all but the more advanced stages of pregnancy. During the first half of the period of pregnancy there is no lipoid in the corpora lutea, which, according to this theory, would account for the pathology in the utuerus following double ovariectomy. If the ovariectomy is performed late in pregnancy, after the lipoid droplets have become quite abundant in the luteal cells, the animal aborts and the uterus undergoes an involution more nearly like the normal, due to the specific effect of the lipoid secretion which is already present in the circulation. Mulon thought the lipoid of the corpus luteum had an antitoxic action toward the poisons elaborated in the development of the fetuses. It would seem more reasonable to suppose that it neutralizes the toxic products produced in normal involution, which would be only a part of its function as a specific agent in effecting this normal involution of the uterus.

It may be added, in closing, that the two luteal secretions are undoubtedly emptied into the blood-stream in these animals. An observation of the elaborate capillary network of these structures could lead to no other conclusion. Lymphatic sinuses are demonstrable in the corpus luteum, but they are found only near the capsule in the proximity of the larger blood-vessels. There is no anatomic evidence for concluding that the secretions are carried away by the lymphatics.

CHANGES IN THE MAMMARY GLAND OF THE ALBINO RAT (MUS NORVEGICUS ALBINUS) DURING THE SECOND HALF OF PREGNANCY*

FRANK L. ROBERTS

The primary purpose of the present study is to determine the changes which occur in the mammary gland of the albino rat during pregnancy, and thereby to establish for this animal a norm which would serve as a basis for experimental work. The subject is old, and much has been written concerning it. But a survey of the literature will show that there has been very little detailed work on the gland during pregnancy on any one animal form, with the exception of Schil's work on the rabbit. Hence it was thought desirable to investigate the subject in the rat, supplementing the researches of Myers, who had worked out the earlier stages of the development of the mammary gland in this animal.

The material comprises the glands of eleven pregnant albino rats (*Mus norvegicus albinus*), primiparae, and two virgin cats; all from the colony in the Institute of Anatomy. The material represents stages from the thirteenth day of pregnancy to within a few hours of delivery and includes the following six stages: thirteen days; sixteen days and twelve hours; eighteen days and twelve hours; nineteen days; twenty days; and twenty days and nine hours. Material for the earlier stages of pregnancy was not available.

The technic of removal and preparation of the glands has been described by Myers[22] which briefly is as follows: The animals were killed with ether; the skin with all the mammary glands was removed immediately and pinned out on a sheet of cork, hairy surface down, and placed in Zenker's fluid.

Cleared preparations were made in the manner described by Myers[22] which is essentially the method Lane-Claypon and Starling used in work on the rabbit. These preparations were mounted in xylol-gum-damar in shallow glass cells.

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In preparing material for microscopic sections, portions of the fixed gland were removed carefully and imbedded in hard paraffin. In sectioning the nipples it was found almost impossible to cut the tough skin when it was imbedded in ordinary paraffin. Therefore Johnston's asphalt method (Guyer), as modified, I believe, by Dr. J. T. Patterson, was employed. Crude rubber was cut into very fine bits with a pair of sharp curved scissors. About three teaspoonfuls of this finely divided rubber were put into a pint of paraffin, melting point 65°C. The mixture was left in the oven for three days and frequently stirred, and by the end of three days most of the rubber had passed into solution; it was then removed from the oven and cooled. A part was melted only when needed for imbedding, since it was soon ascertained that if the mixture is kept melted for much more than three days, the rubber tends to precipitate. This treatment toughens the paraffin to such a degree that the skin imbedded in it can easily be cut.

Sections of the mammary gland and nipple were cut at 3, 4, 5, 7 and 10 microns in thickness. Some sections were stained with Mallory's connective tissue stain; some with Weigert's iron hæmatoxylin, counter-stained with Van Gieson's stain; and some with a 1 per cent aqueous solution of cresyl violet. Another series were stained with Unna's orcein for elastic tissue. A few fresh frozen sections were stained with osmic acid and Sudan III, in order to show the distribution of fat.

The Sudan III stain deserves particular mention because of the beautiful results obtained and because of some of the difficulties encountered in using it. Paraffin sections were passed in the usual way from xylol to water, and from water were placed in the stain for twenty minutes. From the stain the sections, after rinsing well in water, were plunged directly into 95 per cent alcohol for a few seconds; then for the same length of time into absolute alcohol; then into a mixture of absolute and xylol a few seconds; and finally into xylol for three minutes. They were finally mounted in toluol-gum-damar.

The reason for the short treatment with the alcohol and xylol is because it was observed that for some reason the alcohols and xylol quickly decolorize the sections to such a degree that there is no longer any differentiation of the tissue elements.

Cresyl violet, as is well known, gives a most excellent differentiation to the mast cells, sharply marks off the glandular from the connective tissue, and gives very good cytological details.

In studying the increase in the size of the nuclei, cells, and alveoli, a Leitz ocular micrometer was used with a Spencer's mechanical stage. The nuclei measured were those which showed most clearly the nucleolus. The alveoli measured were those in which the lumen was most clearly outlined and nearly circular. The entire alveolus was measured from the base of one cell to the base of the opposite cell. The lumina were measured in their transverse diameters, and the epithelial cells were measured along the diameter perpendicular to the circumference of the alveolus. There was no attempt at extremely accurate measurements as the only thing desired was to determine roughly the change in the size of the alveoli and cells from the thirteenth to the twentieth day.

A few measurements were taken by calipers on the nipples of the pregnant animals and served merely to confirm what could easily be seen with the naked eye, namely, that there is a marked increase in the size of the nipple during pregnancy.

GROSS CHANGES IN THE MAMMARY GLAND DURING PREGNANCY

The only gross change that can be observed externally in the gland of the living animal during pregnancy is the increase in the size of the nipples. If a pregnant rat is suspended by the head or tail the nipples are seen to be very prominent. Part of this prominence is due of course to the stretching of the abdominal skin, but by far the most of it is due to an actual increase in the size of the nipples. This increase in size is apparent to the naked eye and was easily verified by a few rough measurements with the calipers on virgin and pregnant animals.

The increase in the length of the nipple during pregnancy is associated with the complete degeneration of the 'epithelial hood' which surrounds, at least in part, the virgin nipple. Myers[24] has described a partial degeneration of this hood at the time of puberty, but in virgin rats even four months old this hood has not entirely disappeared and is only partly degenerated on one side. During pregnancy, however, the degeneration is completed. At the end of pregnancy there is not a remnant of this hood left, except some necrotic debris in the groove which has taken its place (Fig. 98).

The nipple, accordingly, in pregnant and lactating rats may easily be drawn out to nearly double its apparent length. In fact it is drawn out during the act of suckling, and the purpose of the degeneration of the epithelial hood is doubtless to allow for this increase in the length of the nipple for the accommodation of the young.

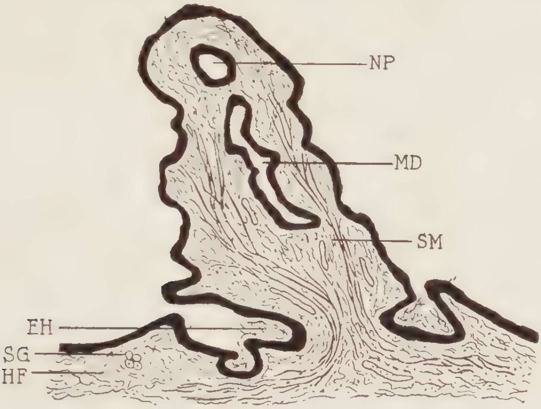

Fig. 98.—Drawing of nipple. Rat sixteen days and twelve hours pregnant. The epithelial hood has entirely disappeared, leaving a groove, *E.H.*, in its place. This groove contains some granular débris, *D.* Well developed smooth muscle, *S.M.*, about the main duct, *M.D.*, of the nipple. The smooth muscle does not extend up to the nipple pore, *N.P.* A hair follicle, *H.F.*, and a sebaceous gland, *S.G.*, are shown on the left. Zenker's fixation, Weigert's iron hematoxylin counterstained with Van Gieson's stain; 7 microns. This section should be compared with Figure 14 in Myers' paper, which shows only a slight degeneration of the hood.

Upon removing the skin from the freshly killed animal, the mammary glands are seen as whitish masses raised slightly above the surface of the rest of the skin. The glands are streaked with numerous blood vessels, which indicate the extremely rich blood supply which the glands have during gestation. The arrangement of the individual glands is best made out with the aid of the cleared preparations.

In the cleared specimens it can be seen that there has been a tremendous increase in the amount of the glandular tissue, which, roughly, forms two horseshoe-shaped masses, anterior and posterior, with their concavities facing each other. This appearance is brought about as follows: There is an overlapping of the glandular tissue of the abdominal and inguinal glands of the same side. The second inguinals of either side overlap across the mid-ventral line of the body and thus the caudal C-shaped mass of glandular tissue is formed.

Likewise there is an overlapping of the three thoracic glands of the same side, and a transverse overlapping of the glandular tissue of the first thoracic glands of opposite sides. There is no overlapping of the last thoracic and abdominal glands, and no transverse overlapping anywhere except in the two regions noted above.

Myers [22] has called attention to this arrangement of the glandular tissue in the virgin animal and the overlapping is merely emphasized by the tremendous proliferation of the glands during pregnancy.

A closer study of the cleared preparations shows that there is one main duct leading to the nipple pore and all the rest of the ducts branch off from this one, as shown by Meyers [22,25]. From the sub-branches of the secondary ducts the buds are seen which in the thirteen-day stage are nearly spherical while they are larger and roughly ellipsoidal in the twenty-day stage.

These bud-like outgrowths on section are seen to consist each of a group of alveoli. Thus each bud represents a lobule, while a secondary duct with its lobules constitutes a lobe. However, it should be noted that the excretory duct of each lobe opens into the main duct before the main duct passes through the substance of the nipple.

Although (as will be shown later) practically no mitoses or amitoses appear in the gland during this period, the cleared preparation in the gland parenchyma of the twenty day stage showed more lobules than that of the thirteen day stage. It is very probable, however, that this represents an individual variation rather than a multiplication of elements in the second part of pregnancy. Some individual variation in the size and arrangement of the mammary glands of the albino rat is always to be expected. This was clearly shown by Myers [22], who was working on rats from the same colony from which the material for this study was taken.

Further evidence that this apparent increase in the number of lobules is due to individual variation is that there is no visible difference in the number of lobules in the glands of the thirteen day stage and those of the sixteen day and the eighteen day stages. The cleared preparation of the nineteen day stage was lost and hence was not available for a comparison, but it is very improbable that a multiplication of the elements would not begin before the nineteenth day of pregnancy. If there were an increase in the number of lobules of the mammary gland in the latter part of pregnancy we would expect to find some evidence of the increase in the time elapsing from the thirteenth day to the nineteenth day stage.

It might be objected that this lack of difference in the stages studied represents an individual variation while the increased number of lobules represent the true condition. In the absence of evidence of cell division, however, I believe it safe to conclude from the material thus far studied that there is probably no increase in the number of glandular elements in the second period of pregnancy, from the thirteenth day onward.

CHANGES IN MICROSCOPIC STRUCTURE

1. *The nipple.*—Aside from the increase in the size of the nipple and the disappearance of the epithelial hood, the main difference in the structure of the nipples of pregnant and virgin animals is in the amount of smooth muscle around the main duct. This smooth muscle, described by Myers [23] in virgin animals, is well developed by the end of pregnancy. Since it is attached externally to the processes of the epithelium which project into the corium of the nipple and internally is continuous with the smooth muscle layer directly under the skin, it is probable that the purpose of this muscle is to aid the elastic tissue in retracting the nipple after it has been drawn out in the act of suckling (Fig. 98). It also may aid in compressing the main duct of the nipple and thus facilitate the flow of milk; but I believe this is rather the minor rôle of this muscle. The emptying of the ducts appears to be rather a passive process, and it seems unnecessary to assume that there must be some muscular elements, as, for example, the myoepithelial cells of La Croix and others, to aid in expelling the secretion.

The lumen of the main duct of the nipple is enlarged considerably during pregnancy. This enlargement is purely mechanical and is due to the increase in the amount of secretion in the duct as pregnancy advances. There is apparently no change in the epithelium of the duct from that in virgin animals, which was accurately described by Myers [24].

2. *General structure.*—A low power view of a section of the thoracic mammary gland of a thirteen day pregnant rat gives a picture which, excluding the panniculus carnosus, represents in general the picture of any one of the mammary glands at any stage of pregnancy. The picture differs from that of a section of a virgin gland in the presence

of lobules, more ducts, more blood vessels, and more cellular elements in the stroma.

A relatively broad band of striated muscle, the panniculus carnosus, is seen running through the center of the section. On either side of this muscle is arranged the glandular parenchyma in the form of lobules and ducts scattered through the fatty tissue. Only occasionally a duct opening directly into a lobule is seen, an appearance which is brought about by the arrangement of ducts and lobules. It is to be remembered that the lobules bud off irregularly from the duct and hence in many places the duct will be cut and not the lobule; in other places the lobule will be apparently isolated, and only when the section happens to cut the narrow stalk connecting the lobule and duct will the true arrangement be seen.

Blood vessels and nerves are scattered throughout the sections. The large nerves lie in close proximity to the muscle, which they supply. The ducts and lobules are surrounded by sheaths of fibrous connective tissue and the rest of the stroma is mostly adipose. In fact the whole picture, excluding the muscle, gives an impression of small islands of glandular tissue in a lake of fat (Fig. 99).

This distribution of the adipose tissue is interesting from the point of view of the development of the mammary gland. Myers has shown that in young albino rats the fat is soon laid down in certain definite regions and into these regional pads of fat the mammary gland pushes its way. Hence we see the explanation for the large amount of adipose tissue in sections of the pregnant gland.

In discussing the finer structure of the gland the following structures will be described in turn: (3) changes in the stroma; (4) changes in the ducts; and (5) changes in the acini.

3. *Changes in the stroma.*—Any stage from the thirteenth to the twentieth day might be described with reference to the stroma and the resulting picture with a few minor changes would represent the stroma of any of the other stages. That is, the stroma is the more constant element in the gland, while the parenchyma is undergoing radical changes.

Each duct is surrounded by a dense sheath of connective tissue, which is prolonged around the lobules which are drained by this duct (Fig. 100). From the lobular sheath, prolongations extend inwards and surround the individual alveoli. Where the sheath leaves the duct to pass around the lobule, it suddenly becomes very much thinner, an arrangement which is easily understood if we refer to Wahl's description of the mode of proliferation of the ducts and lobules.

Here an explanation is given for the appearance of the stroma of the gland after all the lobules and acini are formed. The first bud which pushes out carries with it a covering of fibrous connective tissue derived from the sheath of the parent duct. This bud, enlarging, keeps pushing ahead of it the connective tissue sheath, which as a result becomes very much thinned. Of course this thinning out would not result if the growth of the stroma of the gland kept pace with that of the parenchyma; but Duclert and Steinhaus have clearly shown that the stroma lags far behind the parenchyma as regards growth. None of the specimens studied showed any structure resembling a membrana propria.

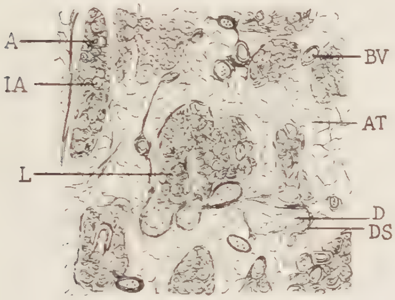

FIG. 99.

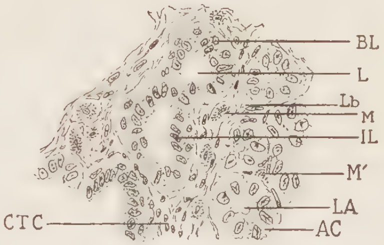

FIG. 100.

FIG. 99.—Drawing (low power) of a section of one of the abdominal mammary glands of a rat eighteen days and twelve hours pregnant. Panniculus carnosus muscle not shown. *BV*, blood vessel; *AT*, adipose tissue; *D*, duct; *DS*, duct sheath; *L*, lobule; *IA*, interalveolar connective tissue; *A*, alveolus. Zenker's fixation; Mallory's connective tissue stain; 5 microns.

FIG. 100.—Section through duct and neighboring acini. Rat fifteen days pregnant. Mast cells and the rapid thinning of the fibrous sheath of the duct are shown, as this sheath passes around the lobule at *LB*. *BL*, basal layer of duct epithelium; *L*, lumen of duct; *M*, mast cell; *M′*, mast cell between two alveoli; *IL*, inner layer of duct epithelium. No vacuolization shown at this stage. *LA*, lumen of alveolus; *AC*, vacuolated alveolar cytoplasm; *CTC*, cellular elements of connective tissue. Zenker's fixation; Cresyl violet stain; 4 microns.

Turning from the covering of the ducts and lobules to the covering of the individual acini, one sees that in the thirteen day stage it is relatively loose (Fig. 101), being composed of elastic and collagenous fibers and traversed by capillaries. By the end of pregnancy, however, the acini have enlarged to such an extent that this sheath has been stretched. As a result it appears more dense and is closely applied to the base of the alveolar epithelium, giving an appearance of a membrana propria.

That this appearance of a membrana propria is a result of the stretching of the interlobular connective tissue and that the membrana propria, as such, does not exist in the mammary gland of the pregnant albino rat, is shown by a study of the stages used for this work. Figure 101 shows that the sheath is loose and only when the acini are distended with secretion do we get the appearance of a basement membrane (Fig. 102). Since the sheaths of the ducts are imbedded in soft adipose tissue, no distention of the ducts stretches the sheath since the adipose tissue yields to the pressure. Hence there is no appearance of any structure resembling a membrana propria around the ducts.

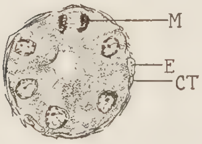

Fig. 101.

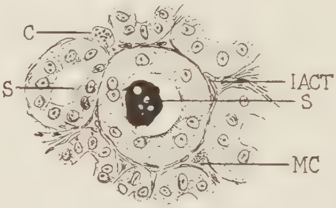

Fig. 102.

Fig. 101.—Alveolus from gland of rat thirteen days pregnant. Connective tissue sheath, *CT*, is relatively loose. Endothelial cell nuclei, *E*, show no pressure effects. Mitotic figure, *M*, shown in one of the cells. Zenker's fixation. Weigert's iron-hematoxylin, counterstained with Van Gieson's stain; 4 microns.

Fig. 102.—Acini from gland of rat, eighteen days and twelve hours pregnant. *IACT*, interalveolar connective tissue is seen to be stretched around the acinus, giving an appearance of a membrana propria. A mass of secretion, *S*, is seen in the lumen of the central acinus. Secretion granules, *S*, are seen being extruded from one of the acinar cells. A distended capillary, *C*, and a mast cell, *MC*, are also shown. Zenker's fixation; Cresyl violet stain; 4 microns.

Besides the prolongations about the lobules, the sheath about the ducts send out projections which become continuous with the sheaths around the blood vessels of this region and everywhere are continuous with the fibrous framework of the adipose tissue (Fig. 99). Where a duct lies next to a muscle, as in the thoracic glands, the sheath around the duct is continuous with the perimysium of the muscle. In the region of the nipple, the ducts merely pass through the subcutaneous tissue and lose the well-defined sheaths which they possess deeper in the gland.

A close study of the sheaths around the ducts, lobules, and acini reveals many elastic fibers in these sheaths. Several authors have attempted to point out a connection between pregnancy and the amount of elastic tissue in the stroma of the mammary gland. As shown in the review of the literature, little has been accomplished towards a solution of the problem. In my material there is an unfortunate arrangement of the age of the specimens. With two exceptions the further advanced the pregnancy the older was the rat. As a result all I can do is to describe the elastic tissue as I found it and to point out some factors suggested by the findings.

In sections stained with Unna's orcein, the elastic tissue fibers are seen to be running lengthwise in the connective tissue sheaths around the ducts, and are prolonged in the form of a few fine fibers around each lobule. From this lobular sheath fine fibrils are sent in which, in the latter stages of pregnancy, surround each alveolus.

In the thirteen day stage, in most cases it is extremely hard to see any elastic tissue round the individual alveoli, but by the end of eighteen days and twelve hours it is easily seen that each alveolus is completely surrounded by a fine network of elastic tissue.

In the earlier stages the elastic fibers are fine and delicate, while in the later stages most of them are exceedingly coarse. The sections show that in the specimens used for this study there is apparently a great increase in the amount of elastic tissue around the ducts from the thirteenth to the twentieth day. This increase is progressive; that is, the fifteenth day stage has more than the thirteen, the eighteen more than the fifteen day stage, and so on.

On the face of it, this would indicate that pregnancy causes a proliferation of elastic tissue in the mammary gland, but as previously pointed out, the age of these specimens, with two exceptions, is arranged parallel with the advance of pregnancy. The representative stages are arranged in the order that the amount of elastic tissue increases and the age of each specimen is indicated:

1. Rat 102, 5½ months, 13 days pregnant
2. Rat 106, 6 months, 15 days pregnant
3. Rat 105, 10 months, 16 days, 12 hours pregnant
4. Rat 101, 3½ months, 18 days, 12 hours pregnant
5. Rat 104, 10 months, 19 days pregnant
6. Rat 103, 9 months, 20 days, 9 hours pregnant
7. Rat 110a, 3½ months, 20 days pregnant.

Between Rats 1 and 2 it was sometimes difficult to determine which had the more elastic tissue, and this was also the case with Rats 5 and

6, but with Rats 1 and 4 there was no question. Rat 4 had much more elastic tissue than did Rat 1, although the former was two months younger than the latter. Rat 110a had much more elastic tissue than Rat 105, and very much more than a virgin rat 12 months old (Figs. 103 and 104).

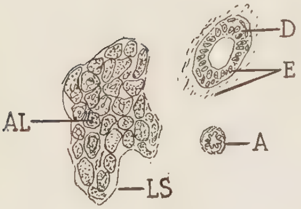

FIG. 103.

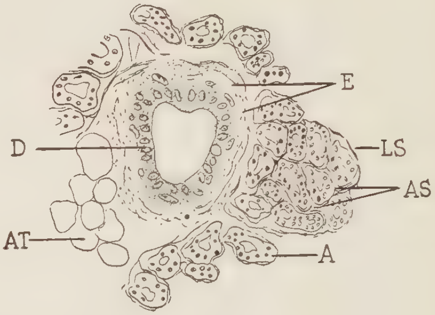

FIG. 104.

FIG. 103.—Sketch showing elastic fibers, *E*, around a duct, *D*. A well defined elastic sheath, *LS*, is seen about the lobule. The alveoli, *AL*, show almost no elastic tissue around them. An arteriole is seen at *A*. Section from gland of a rat five and one-half months old, thirteen days pregnant. Zenker's fixation; Unna's orcein stain; 4 microns.

FIG. 104.—Compare this section with the section in Figure 103. Here there are a great many more elastic fibers, *E*, about the duct, *D*. The lobular sheath, *LS*, is well defined and the acinar elastic sheaths, *AS*, have appeared. An alveolus is labeled at *A*. *AT* is adipose tissue. Section from rat three and one-half months old; eighteen days and twelve hours pregnant. Zenker's fixation; Unna's orcein stain; 4 microns.

With regard to the interalveolar elastic tissue, therefore, one pertinent fact stands out. The alveoli are new formations which appear after the beginning of pregnancy, and hence age can play no direct part in their formation. But during pregnancy, the further advanced the pregnancy, the more prominent do the interalveolar elastic tissue fibers become. The picture thus presented suggests very strongly that pregnancy stimulates the proliferation of elastic tissue in the mammary gland of the albino rat (Bierich).

The adipose tissue was very plentiful in the stroma of the gland in all stages studied, and its distribution and significance have already been referred to under the general structure of the gland.

The stroma of the mammary gland is very rich in cellular elements, many of which are of the wandering type. A great number of these wandering cells are mast cells, which are scattered throughout the stroma, in the connective tissue sheaths around the ducts, in the walls of blood vessels, in the meshes of the adipose tissue, and between the alveoli. It should be noted here that mast cells are not only common in the mammary gland of the albino rat during pregnancy but, according to Downey, are present in large numbers in this animal during its whole life. They are found most plentifully in the subcutaneous tissues, but are also found free in the peritoneal fluid and in the lymph nodes.

Many other wandering cells of leukocytic or lymphocytic type were found in the stroma in all the stages studied. In many cases in which these cells were found between the alveoli it was difficult to decide whether they were inside or outside the capillaries.

Scattered throughout the stroma, but tending for the most part to be located in close proximity to the lobules are many arterioles which send capillary branches in to supply the lobules. These intralobular, or more accurately, interalveolar capillaries are very thin walled and in most places are represented only by endothelial cells. In the thirteen day stage, these capillaries show no distention and the nuclei of the endothelial cells are large and vesicular, showing no evidence of being subjected to pressure. In the sixteen day and twelve hour stage, however, these capillaries are beginning to dilate, and the endothelial nuclei are flatter as a result of the increased pressure from the expanding alveolus. In the eighteen day and twelve hour stage and in the nineteen day stage, the capillaries are greatly dilated. At twenty days and nine hours (a few hours before delivery), they are enormously distended with red blood corpuscles, and the endothelial nuclei are very much flattened.

In regions where striated muscle is seen, large nerve trunks also appear lying in close proximity to the muscle. They are probably destined for the most part to the supply of these muscles. No attempt was made in this investigation to study the nerve supply to the gland substance.

4. *Changes in the ducts.* The epithelium lining the ducts in the mammary gland of the white rat is double-layered throughout. The inner cells are cylindrical or cuboidal, regularly arranged, with their long axes perpendicular to the axis of the duct.

The cells making up the deep or peripheral layer of the duct epithelium are smaller and more irregularly arranged. They are irregularly flattened cuboidal and are arranged with their short axis parallel with the long axis of the inner layer of cells, that is, they tend to encircle the duct (Fig. 105). In many places these cells appear to send processes up for a short distance between the cells making up the inner layer.

In the thirteen day stage, the cytoplasm of the inner layer of duct cells is finely granular, almost homogeneous, and shows no sign of secretory activity. This condition holds true until the sixteen day and twelve hour stage. In this stage a few fine vacuoles can be seen in the cytoplasm of the inner layer of cells. These vacuoles are not numerous but tend to show that secretory activity on the part of these cells has begun.

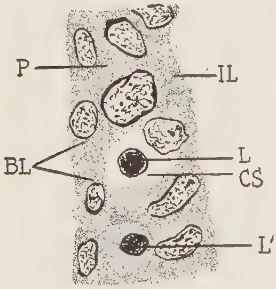

Fig. 105.

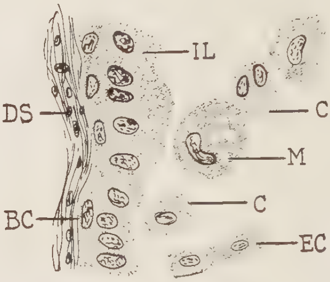

Fig. 106.

Fig. 105.—Section through the wall of a duct of a gland of a rat thirteen days pregnant. The basal layer of cells, *BL*, are shown with a process, *P*, sent up between the cells of the inner layer, *IL*. This section also shows a lymphocyte (?), *L*, in the wall of the duct and surrounded by a clear space, *CS*. Another suspected nucleus is shown at *L′*. Zenker's fixation; Cresyl violet stain; 5 microns.

Fig. 106.—Portion of the wall of a duct and colostrum corpuscles in the lumen from the gland of a rat nineteen days pregnant. *IL*, inner layer of cells showing secretory activity of cytoplasm; *BC*, basal cell. No vacuoles are present in any of the basal cells. *DS*, duct sheath; *C*. colostrum corpuscle with nucleus identical with those of the inner layer of epithelial cells of the ducts; *C′*, colostrum corpuscle with double or fragmented nucleus; *M*, colostrum corpuscle which resembles fatty macrophage. Note crescent shaped nucleus and abundant cytoplasm. *EC*, desquamated epithelial cells still adherent to each other, seemingly end to end. Zenker's fixation; Cresyl violet stain; 6 microns. × 750.

From sixteen days and twelve hours up to within a few hours of delivery the vacuolization of the cytoplasm of the inner layer of epithelial cells becomes progressively more and more pronounced and at the end of pregnancy these cells appear to be actively secreting milk (Fig. 106).

The cytoplasm of the peripheral layer of duct cells is finely granular and almost homogeneous, and even in the last stages of pregnancy these cells show no sign of secretory activity.

In the thirteen and the fifteen day stages, the nuclei of the inner layer of cells are in many places elliptical and in others round. They occupy about the middle of the cell. They are for the most part so crowded that as a consequence there seems to be very little cytoplasm at the sides of the nuclei and the line of demarcation between the individual cells is extremely poorly defined. The chromatin is scattered in the form of granules, more or less uniformly throughout the nucleus, but is not plentiful enough to make the structure look dark. The nuclei are rather vesicular in appearance, but not so much so as the nuclei of the acini, which will be described later. The explanation for the fact that in some places the nuclei appear elliptical and in other places round may be that most of them are actually ellipsoidal, but appear round only when cut transversely to their long axis. After secretory activity begins in the cells of the inner layer, the nuclei of these cells appear to be more rounded and there is more cytoplasm between the individual nuclei.

The nuclei of the deep layer of cells are round, relatively small, and are placed in each case near the center of the cell.

It is these basal cells that have probably been mistaken by many authors (Benda, Berka[3], La Croix and others) for myoepithelial cells. Their shape and the fact that they send up small processes between the cells above them suggest the myoepithelial cells of the sweat glands. Their staining reactions and general appearance however, in the ducts of the mammary gland of the albino rat, indicate that they are merely a basal layer of irregularly shaped and arranged epithelial cells. Some of the more common differential stains (Mallory's connective tissue stain, Van Gieson's stain, and cresyl violet) were used on these preparations, and all of them show conclusively that these cells are epithelial in structure. Whether or not they possess contractile properties I am unable to state, but as mentioned under the discussion on the smooth muscle in the nipple, there seems to be no reason for assuming that these cells must have contractile properties in order to aid in emptying the milk ducts.

5. *Changes in the acini.* The changes in the acini will be discussed in the following order: (a) changes in the size of the alveoli, cells, and lumina; (b) cytoplasmic changes including secretion; and (c) nuclear changes.

The alveoli, in all stages, are lined with a single layer of columnar or cuboidal cells, which are arranged around a central lumen. The lumina of the alveoli increase in size during the latter half of pregnancy, from an average of 5.8 microns in the thirteen day stage to

17.5 microns in the twenty day and nine hour stage. This increase progresses as follows: thirteen days, 5.8 microns; fifteen days, 7.2 microns; sixteen days and twelve hours, 8.0 microns; eighteen days and twelve hours, 19.1 microns; nineteen days, 13.7 microns; and twenty days and nine hours, 17.5 microns.

While these changes were going on in the lumen of the alveoli, the average diameter of the alveoli was increasing as follows: thirteen days, 30.8 microns; fifteen days, 31.0 microns; sixteen days and twelve hours, 32.0 microns; eighteen days and twelve hours, 35.9 microns; nineteen days, 36.8 microns; and twenty days and nine hours, 40.6 microns.

In the same stages, the average height of the epithelial cells was as follows: thirteen days, 11.1 microns; fifteen days, 10.7 microns; sixteen days and twelve hours, 9.3 microns; eighteen days and twelve hours, 8.5 microns; nineteen days, 11.7 microns; and twenty days and nine hours, 12.1 microns.

The foregoing figures represent an average of twenty measurements for each stage. They are only approximate, of course, as the relatively few observations cannot be expected to give more than a rough index of the changes in the successive stages. However, the figures indicate that there has been a marked increase in the size of the lumina of the alveoli, and that there has been an increase in the total diameter of the alveolus, while the alveolar cells have undergone but little change in height.

The explanation for the slight progressive decrease in the height of the epithelial cells in the fifteen, sixteen and eighteen day stages is probably twofold. In the first place, the cells may not have reached their full growth in width and hence are of necessity flattened out when the alveolus is becoming rapidly distended. In the second place the lumina of the acini in these stages are distended to their greatest capacity and the sheaths around them are stretched, it appears, to the limit. At the same time the lumina of the ducts are not so distended in the next stage; however, the ducts are more distended and the amount of secretion in the lumina of the acini seems to have decreased, a result progably brought about by the emptying of the secretion out of the acini into the ducts, thus relieving the pressure on the alveolar epithelial cells. This might permit the increase in height noted at nineteen days and twenty days.

It might be asked here how the acinus could increase in size, the lumina increase in diameter and at the same time the height of the epithelial cells remain practically constant without an increase in the number of these cells? This leads us to the question of mitoses in the gland which will be taken up later. But a count of thirty acini in each stage showed that the average number of cells around the lumina of the acini is eight, —the extremes in a single acinus being six and ten.

The explanation of the increase in the size of the acini with no increase in the number or decrease in the height of the epithelial cells, is that the cells enlarge, lose their high columnar form, widen out, and become low columnar or cuboidal. Thus the acinus can increase in size without an increase in the number of cells lining it, and with no marked change in absolute height.

The increase in the diameter of the entire alveolus is accounted for by the increase in the size of the lumen of the alveolus. The total increase from the thirteenth day to the twentieth day has been 10 microns, and in the same time the lumen has increased 11.7 microns. This discrepancy would probably disappear if a larger number of measurements on more specimens were taken.

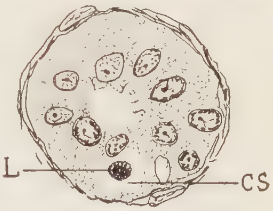

Fig. 107.—Acinus from the gland of a rat thirteen days pregnant. Many fine vacuoles in cytoplasm of the cells are shown. The section is tangential so some of the cells appear to have more than one nucleus. A lymphocytic-like nucleus is shown at *L*. Zenker's fixation; Cresyl violet stain; 6 microns. × 750.

The cytoplasm of the alveolar epithelium of the thirteenth day stage has a foamy appearance, which is due to the presence of a great many fine vacuoles. These vacuoles are for the most part small, round, discrete, and arranged irregularly throughout the cell. As mentioned, they are so great in number and so close together that they give the cytoplasm of the cell the appearance of a fine lacework. In many places some of these vacuoles are seen to be confluent.

By the fifteenth day the vacuolization of the cytoplasm is much more pronounced than in the thirteenth day stage. This appearance is due no doubt to the enlargement of the single vacuoles and the coalescence of many others. As yet there is no sign of any secretion in the lumen of the alveoli or ducts (Fig. 107).

The cytoplasm of the acinar cells in the sixteenth day and twelve hour stage shows merely an exaggeration of the condition in the previous stage, that is, the vacuoles in the cytoplasm are much larger.

In many places one observes what appears to be a "decapitation" of the cells, that is, a detachment of the inner portion adjacent to the lumen. Indeed, as mentioned in the review of the literature, some authors have held that the secretion of the mammary gland owes its origin, for the most part, to such a process.

A careful study of these cells shows, as a rule, one of two things. Either a portion of the section which has been poorly cut, or a location in which a secretion droplet is so large that it has ruptured the cell membrane and carried before it the inner end of the cell, or, rarely, even the nucleus.

With regard to the first possibility it should be emphasized that unless one is extremely careful in all the steps of his technic, the specimen will show various distortions and artefacts. In sections cut with a knife that is slightly dulled one will often get sections in which the whole epithelial lining of a duct is being displaced *en masse*, leaving the naked connective tissue behind, or alveoli will be fragmented and blood vessels ruptured. This, of course, would be an extreme case, but much less distortion might readily produce appearances of "decapitation" in the lining epithelial cells, a fact pointed out by O'Donoghue in the course of his work on the marsupials. In this connection it may be noted that if the tissue happens to be a piece of the gland imbedded while still attached to the skin, and it is cut so that the knife passes through the skin before it passes through the gland, there will be many artefacts which will not be present if the knife passes first through the softer glandular part of the tissue.

With regard to the second possibility, many of the cells contain secretion droplets larger than the nucleus of the corresponding cell. It would seem impossible for such large droplets to get out of the cell without doing at least some damage to the cell membrane. It must be borne in mind that here we are dealing with a condition different from that which obtains in certain mucous cells in which extremely large secretion droplets are formed. In the latter, the nucleus and cytoplasm are pushed to the base of the cell, and the cell membrane, if any, has a chance to regain its integrity before the cytoplasm can be extruded. In the mammary gland cell, however, some of the cytoplasm may be pushed ahead of the secretion droplet and forced out with it. Occasionally, as before mentioned, even the nucleus is carried ahead of the droplet.

Still another fact leads me to believe that this so-called "decapitation" process is accidental and not an essential part of milk formation, and that is, the relative scarcity of such appearances. Indeed the more perfect the section, the fewer of these decapitated cells appear.

In other places in the sixteen day stage one sees a seemingly ragged edge to some of the alveolar epithelial cells next to the lumen, an appearance which is probably due to an actual secretion being extruded from the cell. In this sixteen day stage, there is, in the lumina of the ducts and acini, quite an amount of secretion which is homogeneous, lightly staining, and containing many vacuoles, the result perhaps of dissolving out the fat contained in it.

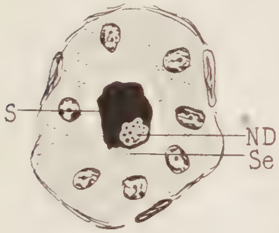

Fig. 108.

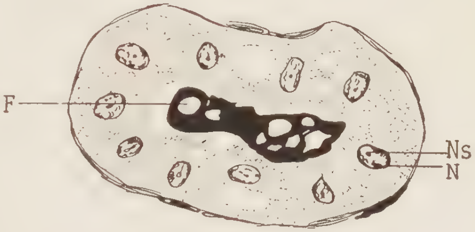

Fig. 109.

Fig. 108.—Acinus from the gland of a rat eighteen days and twelve hours pregnant. Cytoplasm much more vacuolated than in Figure 107. *S*, secretion mass; *ND*, nuclear (?) débris; *Se*, secretion being extruded from cell. Zenker's fixation; Cresyl violet stain; 6 microns. × 750.

Fig. 109.—Acinus from the gland of a rat nineteen days pregnant. Secretion mass with fat vacuoles, *F*, seen in lumen. This secretion shows characteristic arrangement of chromatin in nucleus, *N*. A well defined nucleolus, *Ns*, is shown. Zenker's fixation. Cresyl violet stain. 6 microns. × 750.

The cytoplasm of the acinar epithelial cells is very much more vacuolated in the eighteen day and 12 hour stage than in any of the stages previously described. There are many more of the vacuoles which are larger than the nucleus of the containing cell than there were in the preceding stage. There are also many more examples of secretion granules or droplets being extruded from the alveolar cells (Fig. 108).

In the lumina of the acini, besides the secretion already described, there is some granular débris which by its staining reaction with cresyl violet appears to be of nuclear origin. This débris perhaps comes from the nuclei which have been pushed out by the extremely large secretion droplets in the manner described in the foregoing stage.

Does this nuclear débris give rise to the nucleo-proteins of the milk? It undoubtedly contributes, at least in the stages studied, but as to whether or not it forms an essential constituent of the secretion I am unable to state.

By the nineteenth day the height of the secretory activity of the alveolar cells seems to have been reached, at least no further vacuolization of the cytoplasm is observed. From this stage up to within a few hours of delivery no changes in the cytoplasmic structure of the cells can be observed. There is abundant secretion present in the lumina of the ducts and acini (Fig. 109).

The nuclei of the acinar cells show no observable change during the period from the thirteenth day to within a few hours of birth. These nuclei are about 6.07 microns in diameter, an average of twenty measurements in each stage. Since they do not increase in size as the epithelial cell increases, they appear relatively smaller in the latter stages of pregnancy.

The chromatin of these nuclei has a very definite arrangement. The chromatin masses are arranged around the periphery of the nucleus and a well defined nucleolus in about the center (Fig. 109). This arrangement of the chromatin corresponds to that described by Szabo in the epithelial cells of the active mammary gland of guinea pigs.

Only two unquestionable instances of mitosis were observed in the stages studied. Both of these were in the thirteen day stage (Fig. 109). Furthermore, no definite evidence of amitosis could be observed. The absence of cell division, together with the fact that there is no increase in the number of cells about the alveoli in the stages studied, indicates that the gland has already reached its maximum growth, so far as number of cells is concerned, by the thirteenth day of pregnancy.

6. *Colostrum formation.*—In studying the epithelium of the ducts and acini, nuclei which resembled lymphocytic or leukocytic nuclei were observed in many places. These nuclei were apparently passing through the wall of the ducts and acini. Unfortunately none of the material used in this study had been fixed in Helly's fluid and hence no satisfactory Giemsa or Dominici stain could be used, which would have shown more clearly whether or not these nuclei belong to the blood elements.

There are, however, evidences indicating that these nuclei belong to cells of the wandering type. First, one must bear in mind that there is not a great deal of irregularity in the position of the epithelial nuclei of the ducts or acini, that is, they are about on the same level. These suspected nuclei, however, are usually seen either above or below the level of the epithelial nuclei. They are much smaller and much more densely staining than the nuclei of the epithelial cells, and their chromatin masses, although dense, have fairly definite outlines (Fig. 105). Occasionally they are surrounded by a clear space and in one case at least presented a definite, pale green, narrow rim of surrounding cytoplasm, in a section stained with cresyl violet.

Since these sections were stained with iron haematoxylin or cresyl violet, it is possible that the nuclei might be pycnotic epithelial nuclei. If they were, however, one would not expect to see the chromatin masses so clearly outlined and the whole nucleus should appear more uniformly shrunken and black in color. Their position, the appearance of their chromatin, and their relation to the epithelial cells, all point strongly to the conclusion that these nuclei belong to wandering cells.

There are other more general phenomena which support this conclusion. Leukocytic infiltration of the gland has been observed by various investigators in several other species, in the first half of pregnancy. The stroma is rich in cellular elements in the second half of pregnancy and (as noted in the literature) in several other forms leukocytes and lymphocytes have been found a constant constituent of colostrum.

So far as this study goes, all I am able to state is that my material does not prove that these nuclei are of the wandering cell type, but the appearance they present strongly indicates this conclusion. As previously mentioned, sections with specific blood stains must be carefully studied before a final conclusion is justified.

This leads to a consideration of the origin of colostrum corpuscles in the rat. In the lumina of the ducts, less often of the acini, in the latter stages of pregnancy fatty cells are observed which are lying free in the mass of secretion. These cells begin to appear in the sixteen day and twelve hour stage and increase in number from then until the end of pregnancy. Previous to the sixteen day and twelve hour stage a few desquamated epithelial cells were observed in the lumina of the ducts, but since they were not fatty they do not represent true colostrum corpuscles. The cells in the latter stages are in most cases as large as the epithelial cells of the gland; they have many fatty vacuoles, and the nucleus for the most part is large, round, and vesicular, appearing identical with the nuclei of the epithelial cells. In other cases, these cells are smaller, the cytoplasm is not quite so vacuolated, and the nucleus resembles that of a leukocyte or lymphocyte. A third class of these cells, which occur more rarely, resembles macrophages, in that they have a crescent shaped nucleus and abundant, lightly-staining cytoplasm, filled with a great many vacuoles. The various types of colostrum corpuscles may be seen in Figure 106.

What is the origin of these cells? I have already discussed the probability that the cells resembling lymphocytes and leukocytes might actually be such, which have wandered through the walls of the ducts and acini. Such cells, either in the lumina of these structures or before they pass through their walls, may have become laden with fat, although no fatty leukocytes were observed anywhere in the stroma.

The origin of those occasional cells which resemble macrophages, cannot be determined definitely. The different shape of the nucleus might be accidental or due to some degenerative process. However, Professor Downey, who kindly examined some of my preparations, called my attention to the presence of large, apparently phagocytic cells in the interalveolar spaces. A careful study with special stains might possibly show that these large phagocytes occasionally pierce the walls of the ducts or acini. The nuclei of the large interalveolar cells appeared rounded, however, rather than crescent shaped, as found in the intra-alveolar cells. But the nucleus is often variable in this type of cell (Fig. 110).

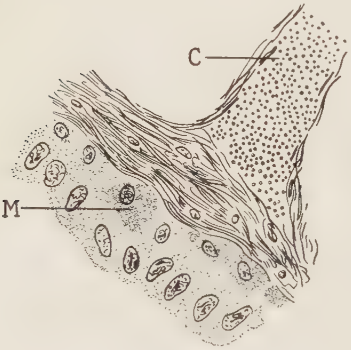

FIG. 110.—Portion of the wall of a duct of the gland of a rat nineteen days pregnant. A large cell, *M*, is seen in the wall of the duct. This cell has staining reaction different from that of the epithelial cells. The cell might possibly be a macrophage. *C* represents a greatly distended capillary. Zenker's fixation; Mallory's connective tissue stain; 7 microns. × 300.

Most of the colostrum corpuscles, however, are undoubtedly desquamated cells derived from the epithelium of the ducts and acini. I have been able to trace them in all stages from the beginning of their desquamation to the time they have become rounded, fully formed colostrum corpuscles. Some appear breaking off from the epithelial wall but still partly attached. Others are lying close to the wall of the duct, but still maintaining a more or less cubical shape. Finally they appear as rounded cells, this shape being assumed when the cells become free in a liquid medium. These stages, may be seen in Figure 111.

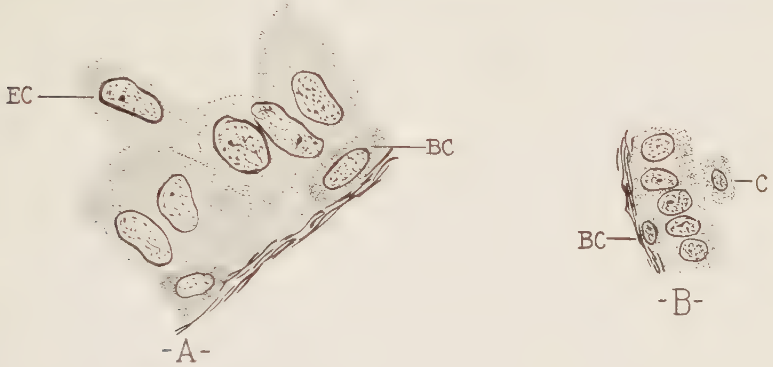

FIG. 111.—A section through the wall of a large duct of the gland from a rat eighteen days and twelve hours pregnant. Epithelial cell, *EC*, being desquamated. Basal cells shown at *BC*. *B*, wall of smaller duct from same section. Epithelial cell, *C*, shown free in the lumen; it has not yet lost its cylindrical shape. *BC*, basal cell. Zenker's fixation; Mallory's connective tissue stain; 6 microns. × 750.

Occasionally two adjacent cells may be detached at the same time, lying free in the lumen of the duct although still remaining attached to each other (Fig. 106).

Further evidence that these cells are epithelial in origin is shown by the fact that when they are observed in the ducts of the sixteen day and twelve hour stage they are not as vacuolated as they are later. In other words the cytoplasm of the earlier colostrum corpuscles is in the same condition as that of the epithelial cells lining the ducts. The nuclei, with the exception of the crescent shaped, and the smaller, probably leukocytic, nuclei, appear in most cases identical with the epithelial nuclei.

The scarcity of these cells in the lumina of the acini, indicates that by far the greater number of them come from the duct epithelium.

It should be emphasized that this desquamation of epithelial cells is not a pathologic condition, nor is it an artefact due to faulty technic I have excluded all cases in which there is an extensive desquamation of cells, or in which the walls of the ducts, acini, or blood vessels indicate a previous injury or abnormality. Only those cases were chosen for study in which the gland appeared perfectly normal in structure.

Before leaving the question of the origin of colostrum corpuscles, we may consider the theory of Steinhaus and Unger, according to which mast cells are thought to be transformed into colostrum corpuscles. Attention has already been called to the large number of mast cells in the stroma of the mammary gland of the albino rat during pregnancy. That this is a fairly constant occurrence in other forms, as well as in the rat, is indicated by the reports of Unger, Steinhaus, Michaelis, Berka, and Bizzozero and Ottolenghi.

Steinhaus, after describing the number and appearance of the mast cells in the mammary gland of the pregnant guinea pig, concludes that the colostrum corpuscles represent "einfach Mastzellen mit verfettenen eosinophilen Körnern." A close study of my data, however, fails to show a single mast cell undergoing fatty metamorphosis, or passing through the walls of the ducts or acini, or in the lumina of these structures. Furthermore the granules of mast cells are obviously not eosinophilic.

Unger is more definite in his statements regarding the relation of mast cells to colostrum. He found these cells in the glands of human beings and guinea pigs, in large numbers around the blood vessels and ducts, between the fat cells in the retromammary fat tissue, between the alveoli and sending up processes between the epithelial cells, in the perialveolar lymph and blood spaces, and in the axillary and retromammary lymph nodes. He claims to have demonstrated fat granules in the bodies of these cells, but other authors, particularly Bertkau and Berka have since questioned whether these cells were actually mast cells.

Unger concludes by approving Czerny's theory of the leukocytic origin of colostrum corpuscles, but goes farther in ascribing to the mast cells the major rôle in this process.

Berka, however, in discussing the theory, states that the mere presence of these mast cells in the gland during pregnancy does not prove that they aid in forming colostrum. Furthermore he was unable to demonstrate fat in any of the mast cells.

In the case of the rat, it is an easy matter to settle this question, for in the rat are mast cells in great numbers. Their distribution has already been described under stroma (Fig. 100).

If the mast cells take any part in the formation of colostrum, evidence should appear in the following respects: (1) If the mast cells undergo fatty metamorphosis, this process should appear even in ordinary stained sections, (2) some of these cells should be seen passing through the walls of the ducts or acini, and (3) some of them should be seen free in the lumina of these structures.

In a careful study of hundreds of sections, I have not seen a single mast cell undergoing fatty metamorphosis and in no case was a mast cell observed in the walls of the ducts or acini or within the lumina. It is therefore certain that in the rat at least, mast cells take no direct part in colostrum formation.

The picture presented, then, is one in which there is an increasing number of cellular elements in the secretion of the mammary gland as pregnancy advances. These cells present various stages of fatty vacuolization and represent true colostrum corpuscles. The following conclusions, therefore, appear justified on the basis of the evidence which has been presented:

1. Colostrum corpuscles in the rat are independent nucleated cells. This confirms the view of practically all modern investigators with the exception perhaps of Benda, who regards free cells in the lumina of the ducts and acini of the mammary gland as artefacts.

2. Colostrum corpuscles originate for the most part from desquamated epithelial cells. This agrees with the conclusions of Reinhardt, von Beuren, Will, Scanzoni, Sticker, Kehrer, Langer, de Sinety, Buchholz, Coen, Kadkin, and Palazzi, but disagrees with Rauber, Saefftigen, Czerny, Benda, Steinhaus, von Ebner, Unger, Cohn and Bab.

3. Some of the colostrum corpuscles may arise from immigrated lymphocytes or leukocytes. Palazzi, so far as I know, is the only author who calls specific attention to the double origin of colostrum corpuscles.

4. Mast cells play no direct part in the formation of colostrum corpuscles. This is in agreement with the conclusions of Cohn and Berka,[4] and opposed to the claims of Steinhaus and Unger.

TWO PRINCIPAL PHASES

The picture presented by the mammary gland of the albino rat in the latter part of pregnancy is that of a gland which has already reached its maximum growth, so far as a multiplication of elements is concerned. From the thirteenth day on, any enlargement is due chiefly to a mechanical distention of the hollow structures of the organ, together with hyperemia, although there is also hypertrophy of the glandular cells.

The gland is undergoing striking histologic changes, which are directed towards the elaboration of secretion. As a result, the parenchyma is the part of the gland that is changing, while the stroma (aside from the increased vascularity) remains practically unchanged, except secondary changes due to pressure associated with the growth and expansion of the parenchyma.

The secretory activity of the gland is evidenced by a hypertrophy of the glandular elements. The acini increase in size, their lumina enlarge, and their epithelial cells become much larger. The cytoplasm of the epithelial cells becomes progressively vacuolated, first in those of the acini, and later in those lining the ducts. The cells remain clearly outlined and do not lose their definite form, and the nuclei do not change in position or appearance. These facts indicate that the cytoplasmic vacuolization is the result of the secretory activity of the cell, and is not a sign that the cell is undergoing fatty metamorphosis or necrobiosis.

Two stages can therefore be recognized in the changes of the mammary gland of the albino rat during pregnancy. These two phases, as described by Bouin and Ancel and Schil, in the rabbit, are (*a*) a phase of growth activity, and (*b*) a phase of secretory activity. The first, which occurs in stages earlier than those covered in the present paper, is marked by the addition of new elements, an increase in the number of ducts and lobules, and an infiltration of lymphocytes and leukocytes. The second phase begins in the latter half of pregnancy, the period studied in the present investigation. Here the epithelial cells begin to elaborate secretion and from now on any growth is due chiefly to cellular hypertrophy and enlargement by accumulation of secretion and by hyperemia. At the same time the leukocytic infiltration is becoming progressively less prominent. The formation of colostrum also falls within this period.

SUMMARY

The conclusions from a study of the mammary gland in the albino rat from the thirteenth to the twentieth day, or end of pregnancy, may be summarized briefly as follows:

1. The nipple increases in size during pregnancy, but has apparently reached its maximum growth by the thirteenth day. The

epithelial hood about the nipple entirely disappears during pregnancy, resulting in an elongation of the nipple, and at the same time the smooth muscle about the main duct has become well developed.

2. The stroma, aside from progressive increase in the blood vessels, and an increase in the elastic tissue, especially around the ducts, shows no marked changes. There is no membrana propria around the acini, aside from a thin connective tissue sheath formed by their distention.

3. There is a tremendous proliferation of the mammary parenchyma during pregnancy. Hyperplasia is evidently confined chiefly to the first half of pregnancy, as mitosis is rare from the thirteenth day and amitosis apparently absent. The ducts and acini continue to increase in size, however, partly through hypertrophy of the epithelial cells, and partly by accumulation of secretion within the lumina.

4. Progressive cytoplasmic vacuolization, indicating secretory activity, is apparent in the acinar epithelium from the thirteenth day, and some days later in the cells lining the ducts. The maximum degree of vacuolization is reached by the nineteenth day. "Decapitation," or detachment of the inner portion of the acinar cells during secretion, is a rare occurrence and does not represent the usual mode of secretion in the stages observed. The secretory cells usually remain intact.

5. Colostrum corpuscles are derived chiefly from desquamated epithelial cells of the ducts and acini. Some may be derived from immigrated lymphocytes or leukocytes. Mast cells are abundant in the stroma, but take no direct part in the formation of colostrum corpuscles.

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III

DUCTLESS GLANDS

THE MORPHOGENESIS OF THE FOLLICLES IN THE HUMAN THYROID GLAND*

EDGAR H. NORRIS

The complicated process of morphogenesis of the follicles of the prenatal human thyroid gland is worked out by graphic and wax-plate methods of reconstruction and several mooted points definitely established by the study of fifty human embryos and fetuses of from 6 mm. to 163 mm. crown-rump length, several fetuses in later stages, and newborn.

The summary of the results is as follows:

1. The so-called "cords" forming the anastomosing network in sections of the thyroid (median anlage) in the latter prefollicular stages represent chiefly sections of epithelial bands, two cells in thickness, and forming irregular, fenestrated plates.

2. The frequently described stage in which the "cords" are transformed into an anastomosing set of epithelial tubes from which the follicles are derived does not exist. The process of follicle formation gives no evidence or indication that the thyroid has been derived from a branching tubular gland.

3. The primary thyroid follicles arise directly as isolated and independent structures from the epithelial plates of the pre-follicular period, by the rearrangement of cells, cell proliferation, increase in the size of the cells, and lumen formation.

4. The primary follicles appear in fetuses about 24 mm. in length. The epithelial bands (fenestrated plates) have practically disappeared in a fetus of 65 mm., but a few solid interfollicular epithelial masses are still present in fetuses 163 mm. in crown-rump length.

5. Secondary thyroid follicles are formed from pre-existing follicles apparently by three methods: by solid buds; by hollow buds; and by constriction of the parent follicle.

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6. The first secondary follicles appear in fetuses about 56 mm. in length, but are formed most rapidly in stages when the fetus is between 80 mm. and 158 mm. long. After 163 mm., the growth of the gland probably takes place largely by the increase in size of the individual follicles, rather than by the increase in their number.

7. Large cystic follicles were observed in the lower and posterior (dorsal) parts of four glands from the older fetuses. Their significance is uncertain, as is likewise the apparent involution of the follicles with desquamation of epithelium observed in the later fetal and in newborn stages.

THE INFLUENCE OF PARTIAL THYROIDECTOMY IN PIGS*

CHARLES C. PALMER

The influence of partial thyroidectomy in pigs was studied by the removal of the thyroid glands from three pigs (one female and two males) at the ages of eight, twelve, and fifteen days, respectively. Three other pigs (one female and two males) from the same litter served as controls.

The extirpation of the main thyroid gland did not induce cretinism, at least within a period of nearly one year. There was a slight retardation in growth, but the pigs operated on appeared similar to the controls, except that they showed a marked lowered resistance to infection.

Postmortem examination of the thyroidectomized pigs revealed a marked hypertrophy of the accessory thyroid tissue.

The conclusions from this study are:

1. The main thyroid gland plays an important part in the normal body resistance to infection and when this structure is removed the accessory thyroids cannot compensate completely.

2. In pigs a degree of hypothyroidism, not sufficient to lead to marked changes in the physical appearance of the animal, markedly lowers the resistance to infection and apparently impairs the functions of reproduction.

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THE GROWTH OF THE BODY AND ORGANS OF THE ALBINO RAT AS AFFECTED BY FEEDING VARIOUS DUCTLESS GLANDS (THYROID, THYMUS, HYPOPHYSIS, AND PINEAL)[*]

ELMER R. HOSKINS

In this study on the relations of some of the ductless glands to the growth process in albino rats, twenty-nine litters of rats were used, (fifty-nine females, seventy-three males). In most cases, the experiments began when the rats were weaned, at the age of three weeks, a few later. The test rats were fed on alternate days with various dosages of either the fresh (in nine litters) or the dried glandular substance, from newly-killed calves six to ten weeks of age. The material was fed mixed with graham bread and whole milk. The controls (one of each sex from each litter) were fed the bread and milk, with the addition of fresh beef-muscle equivalent in weight to the dosage of gland-substance fed the test rats. The body weights were taken at frequent intervals. The animals were killed and necropsied at various ages, from ten weeks up to the adult. The various organs and parts were carefully weighed.

Some of the principal results and conclusions of the experiments may be summed up briefly as follows:

1. The normal growth of the albino rat varies materially, not only in different "strains" and under different conditions of environment, but even among litters when all conditions are as nearly constant as possible. It is therefore not sufficient to rely on the established forms of growth for comparison, but in all cases experimental and control animals should be selected of the same sex and from the same litter or litters.

2. In the case of rats with unusually rapid (or slow) growth, in addition to comparison with older or younger rats of corresponding size

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and weight, due regard for possible changes correlated with age must be observed. Such changes have previously been noted in the water content of the nervous system (Donaldson), weight of the thymus (Hatai), and probably the weight of the eyeballs (Jackson). Indications of similar age-changes independent of body weight are found in the skeleton, liver, kidneys, heart, and spleen. Compared with animals of the usual age at a given body weight, the skeleton seems to be relatively heavy in older animals, and the other organs are apparently heavier in younger rapidly growing animals.

3. There is apparently no sexual difference in the relative weight of the pineal body, such as has been found in the suprarenal glands (Jackson, Hatai) and the hypophysis (Hatai).

4. Thyroid feeding (in sub-toxic doses) causes little or no change in body weight in growing rats. There is possibly a slight stimulation in growth of the body as a whole, balanced by a decrease in the amount of free fat in the body. There is a slight loss in the relative weights of the eviscerated body and the integument, probably due to loss of body-fat.

5. Thyroid feeding produces a decided hypertrophy of the heart, liver, spleen, kidneys, and suprarenal glands, especially in males. It apparently causes also a somewhat less extensive and more uncertain increase in the weights of the alimentary canal and hypophysis (male) and possibly in the skeleton, testes and epididymi, and a decrease in the weight of the hypophysis of females.

6. Thymus feeding (with the dosage employed) has no apparent effect on the growth rate of the body of albino rats. No constant or important effect on any of the individual organs or parts was observed. The testis showed no degenerative or other changes.

7. Hypophysis feeding (entire gland, with the sub-toxic dosage employed) produces no marked or constant effect on the growth rate of the body or organs of albino rats.

8. Pineal feeding likewise produces no apparent changes in the weight of the body or organs of the albino rat, beyond differences probably within the limits of normal variation.

THE HISTOGENESIS OF CARCINOMA IN THE ISLETS OF THE PANCREAS*

EDMUND J. HORGAN

The earliest stages of carcinoma have been found in association with chronic inflammatory changes in many organs in the body; therefore it seemed theoretically possible that similar neoplastic changes might be found in association with chronic pancreatitis. The author examined 262 pancreases which were removed at necropsy from patients who died from ulcer of the stomach, ulcer of the duodenum, cholecystitis with stones and cholecystitis without stones, cholangitis with stones and cholangitis without stones, and carcinoma of the stomach, of the liver, of the gallbladder, and of the bile ducts. The pathologic conditions noted were acute and chronic pancreatitis, stages of fat necrosis, simple cysts, cystadenomas, papillary cystadenomas, and hypertrophy and hyperplasia in the islets of Langerhans. Of these conditions, hypertrophy and hyperplasia in the islets in chronic pancreatitis were selected as the subject of this special investigation. A study of the normal development and structure of the pancreas was also made.

Hypertrophy of the islets in connection with chronic pancreatitis was found in forty-eight of the 262 pancreases. Seventy-nine and three-tenths per cent of these forty-eight were found in cases in which a gastric or duodenal ulcer was found at operation or at necropsy. The islets showed hypertrophy in twenty-five per cent of the gastric ulcers and in 31 per cent of the duodenal ulcers. Hypertrophy of the islets was observed in 18.1 per cent of the cases of associated gastric and duodenal ulcers. The hypertrophy was noted in association with several other conditions. The size of the hypertrophic islets varied from 0.5 mm. to 6.0 mm. in diameter. Usually they were found in great numbers. The connective tissue in the islets was always in-

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creased and the capsule surrounding the islet was always thickened. Hypertrophic and hyperplastic cells were found in these islets, and in a few migration of these hyperplastic epithelial cells had taken place; they passed through the three successive stages of neoplasia:

Primary cytoplasia.—Most of the epithelial cells are differentiated, some are hypertrophic and the outline of the cytoplasm in these is not well defined. These islets have a thickened connective tissue capsule and a diffuse fibrosis throughout.

Secondary cytoplasia.—The epithelial cells are undifferentiated or partially differentiated. Some of the undifferentiated cells are hypertrophic. The number of epithelial cells is increased markedly, but all the cells are confined within the connective tissue capsule.

Tertiary cytoplasia.—The epithelial cells are undifferentiated; some, however, in some islets show partial differentiation. They are hypertrophic and hyperplastic and there is a marked increase in size and number. Migration of the epithelial cells through the connective tissue may be seen at the periphery. This migration of the epithelial cells is evidence of a carcinoma. The islets are very large, the largest being 4 mm. by 6 mm.

Hypertrophy of the islets and adenomas of the islets are the only conditions reported in the literature which could be considered precancerous. Hypertrophy has been reported mostly in connection with diabetes. It is not characteristic of diabetes, however, and it is not found in all cases of diabetes. It is not reasonable to assume that all neoplasms in a mixed gland, like the pancreas, originate in one only of its three epithelial units. It is more logical to assume that a neoplasm may originate in any one of the epithelial units, the ducts, the acini, or the islets. From a biopathologic point of view the histogenesis of neoplasia of the pancreas should be studied in each of these. Under suitable pathologic conditions, each epithelial unit could be expected to produce undifferentiated cells from its germinative tissue; but the study must be made from the tissues which show the changes antecedent to carcinoma. When neoplasia is well advanced or has caused death, it is impossible to establish the site of origin or the successive pathologic changes from the tissue removed at operation or at necropsy; it is because pathologists have tried to prove the histogenesis from tissue removed at necropsy, after malignancy has caused death, that the histogenesis of carcinoma of the pancreas has not been established.

The histogenesis of carcinoma of the pancreas must be studied from portions of the pancreas which are too small to be recognized in the gross specimen as carcinoma. For this reason a series of cases showing chronic inflammation was selected for the study of the early neoplastic changes. In the course of the investigation definite hypertrophy and hyperplasia were found of the islets of Langerhans. In these hypertrophic islets hypertrophy, hyperplasia, and migration of the cells were observed.

In the hypertrophic islets hypertrophic differentiated cells were found. Accompanying this cellular hypertrophy the connective tissue within the islets and surrounding the islets had increased to protect the adjacent cells from encroachment.

In similar islets hyperplasia of undifferentiated epithelial cells was also found. These undifferentiated cells, however, are distinctly confined within the dense capsule of the islet.

In some of the hypertrophic islets hyperplastic undifferentiated cells were found migrating through the capsule, a condition which is undoubtedly carcinoma.

The biologic reactions in the epithelial cells of the islets in the pancreas conform to those that have been observed in epithelial cells in other tissues and support the argument that each organ should be studied from the standpoint of each histologic unit, and that each histologic unit must be considered alone from the standpoint of regeneration in all its phases.

A PREOPERATIVE AND POSTOPERATIVE STUDY OF DIABETIC PATIENTS WITH SURGICAL COMPLICATIONS*

DAVID M. BERKMAN

In 1915 I published a short paper on diabetes based on the study of a series of twenty-six patients who came to operation with a total mortality of 7.7 per cent. Since I wished to learn if our results continued to bear out the conclusions made in 1915 I have made a study of a much larger series, and the findings compare favorably with those in the earlier report. In considering the low mortality rate four significant factors should be borne in mind: (1) we have been forced to operate on very few patients with acute diabetes before bringing the diabetes under control; (2) light ether anesthesias have been given by the open nonasphyxiating method; (3) we have adhered to a program of selection and have attempted to eliminate from surgical procedures patients who have been demonstrated impractical risks from the standpoint of diabetes; and (4) most of our patients have had a mild form of diabetes. On the other hand, a large proportion of the patients have had major operations for serious conditions.

If the literature is reviewed from the standpoint of vital statistics very few observations are found based on a series of cases large enough to be conclusive. In my previous paper I referred to the series of cases collected by Phillips from the literature in which there was a mortality of 17.7 per cent in cases previously treated for diabetes. In Karewski's series of 136 cases there was a mortality of 16 per cent. The mortality in part of this series was 20 per cent (Addis). The mortality in operations on infected tissue was 21.7 per cent, in operations on uninfected tissue, 11.8 per cent. Fitz has recently reported a 28.7 per cent mortality in a series of forty-five cases. The mortality rate among the infected cases was 50 per cent, among the noninfected cases it was 12 per cent. It is scarcely necessary again to call attention to the very apparent increase of risk when there is infection at the site of operation.

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The series herein reported comprises 159 separate operations performed on 134 persons. There were eight deaths from all causes; two patients died in coma, presumably of diabetic origin. The mortality based on 159 operations was 5.03 per cent, 25 per cent in coma; based on 134 patients it was 5.97 per cent. I am including tables of the findings of the patients under discussion with the pertinent data (Tables 1 and 2). The classification of the severity of diabetes has been made with special care not to designate as a severe case in which observation under a dietary regime did not reveal an exceptionally low carbohydrate tolerance.

TABLE NO. 1

One hundred and fifty-nine operations on diabetic patients.

Case	Age	Sex	Degree of diabetes	Operation		Sepsis	Anesthetic
115441	50	F	Mild	9–22–14 9–29–14 5–19–15	Ligation left superior thyroid artery Ligation right superior thyroid artery Thyroidectomy	0 0 0	Local Local Ether and local
119774	58	F	Moderately severe	12–22–14 8–17–15	Enucleation right eye, Percy cautery to orbit for extensive cancer involving lids, canthus and eyeball Excision with Paquelin cautery two small epitheliomas outer canthus right eye	0 0	Ether Local
143189	33	M	Moderately severe	1–16–15 1–21–15 12–14–15	Ligation left superior thyroid artery Ligation right superior thyroid artery Thyroidectomy	0 0 0	Ether Local Ether
122620	44	M	Mild	1–22–15 1–29–15 5–14–15	Ligation left superior thyroid artery Ligation right superior thyroid artery Thyroidectomy	0 0 0	Local Local Ether and local
122798	53	F	Moderately severe	1–29–15	Cholecystostomy, drainage pancreatic cyst	0	Ether
123150	46	F	Mild	2– 1–15 2–11–15 6–14–17	Choledochotomy, cholecystectomy, appendectomy Choledochotomy, removal stones Choledochotomy, removal stones	+ + 0	Ether Ether Ether
124214	36	M	Mild	2–27–15	Posterior gastrectomy for duodenal ulcer	0	Ether
126765	55	M	Moderately severe	3–29–15	Circumcision, hemorrhoidectomy	0	Local
129852	60	F	Severe	5–20–15	Extraction of cataract with iridectomy, left eye,	0	Local
129873	64	F	Mild	5–25–15	Cholecystectomy	0	Ether
131911	39	F	Mild	6– 1–15	Tonsillectomy	+	Local

* Patient died in hospital.

Table No. 1—(Continued)

Case	Age	Sex	Degree of diabetes	Operation	Sepsis	Anesthetic
131543	66	F	Mild	6– 9–15 Radical amputation of breast for cancer	0	Ether
132286	42	F	Mild	6–11–15 Cholecystectomy, appendectomy	0	Ether
133451	31	M	Moderately severe	6–28–15 Inguinal herniotomy	0	Ether
133835	44	F	Mild	6–30–15 Abdominal hysterectomy, fibroid uterus	0	Ether
134005	47	M	Moderately severe	7– 7–15 Excision of cancer of right brow	0	Local
133918	58	F	Mild	7– 7–15 Removal of double ovarian cyst, both ovaries and tubes; appendectomy	0	Ether
130169	55	F	Severe	7– 8–15 Thyroidectomy	0	Ether
134774	63	F	Mild	7–12–15 Mikulicz-Hartman-Bilroth No. 2 for cancer of the stomach	0	Ether
769	49	F	Mild	7–27–15 Herniotomy, umbilical hernia	0	Local
136721	62	M	Mild	7–31–15 Suprapubic drainage of the bladder	0	Local
138001	53	F	Severe	8–20–15 Thyroidectomy	0	Local
141126	59	M	Severe	10–14–15 Tapping of hydrocele	0	Local
146905	44	F	Mild	12– 9–15 Excision of tumor submaxillary glands, cancer	0	Local
147832	42	M	Moderately severe	12–22–15 Hydrocele	0	Ether
147472	26	F	Mild	12–28–15 Appendectomy	0	Ether
149076	55	F	Moderately severe	1–25–16 Exploration, general cancer	0	Ether
150542	35	F	Moderately severe	2–18–16 Cholecystectomy	0	Ether
152350	52	F	Mild	3– 9–16 Thyroidectomy	0	Ether
62967	49	M	Mild	3–15–16 Gastro-enterostomy for duodenal ulcer	0	Ether
154837	55	F	Mild	3–25–16 Thyroidectomy	0	Ether
154524	17	M	Mild	3–28–16 Appendectomy	0	Ether
154245	55	M	Severe	4– 3–16 Cholecystectomy	0	Ether
156163	50	F	Mild	4–10–16 Tonsillectomy	+	Local
157981	55	M	Mild	5– 3–16 Cholecystectomy	+	Ether
158189	68	M	Mild	5–13–16 Circumcision	0	Local
159072	50	M	Mild	5–24–16 Cataract, right eye	0	Local
160174*	29	M	Mild	5–26–16 Tonsillectomy	+	Local
154378	54	F	Mild	5–30–16 Thyroidectomy 6–14–16 Herniotomy, umbilical hernia enucleation fibroid of cervix	0 0	Ether Ether
161937	31	M	Mild	6–20–16 Tonsillectomy	+	Local
163419	60	M	Mild	6–28–16 Hydrocele	0	Ether
160363	56	F	Mild	7– 4–16 Right nephrectomy, hypernephroma	0	Ether
162827	41	M	Severe	7–10–16 Ligation left superior thyroid artery 7–14–16 Ligation right superior thyroid artery	0 0	Local Local

* Patient died in hospital.

Table No. 1—(Continued)

Case	Age	Sex	Degree of diabetes	Operation	Sepsis	Anesthetic
162661	60	F	Mild	7–12–16 Perineorrhaphy	0	Ether
163382	40	M	Mild	7–14–16 Pyloroplasty for duodenal ulcer	0	Ether
170710	70	M	Mild	9– 1–16 Removal sequestrum right femur	+	Ether
170844	33	F	Mild	9– 5–16 Ligation left superior thyroid artery 9–11–16 Ligation right superior thyroid artery	0 0	Local Local
172215	57	M	Mild	9–14–16 Cholecystectomy, appendectomy	0	Ether
171566	64	M	Mild	9–21–16 Sick operation for hydrocele 3–12–19 Extraction cataract right eye	0 0	Local Local
172978	58	M	Mild	9–26–16 Thyroidectomy	0	Ether
124544	57	F	Mild	9–27–16 Hysterectomy, cancer uterus	0	Ether
55399	43	M	Mild	10–27–16 Tonsillectomy	+	Local
175259	19	F	Mild	11– 1–16 Appendectomy	+	Local
176239*	55	F	Mild	11– 3–16 Thyroidectomy	0	Ether and local
170213	39	F	Moderately severe	11– 8–16 Abdominal hysterectomy	0	Ether
179567	57	F	Mild	12–20–16 Cholecystectomy	0	Ether
180444*	61	M	Mild	12–26–16 Herniotomy, inguinal	0	Local
183072	34	F	Mild	1–18–17 Bunion removed, right foot	0	Ether
182594	59	M	Mild	1–22–17 Submucous resection	0	Local
183515	59	F	Mild	1–29–17 Abdominal hysterectomy, cancer of uterus 2–15–17 Cholecystectomy	0 0	Ether Ether
183967	39	M	Mild	2– 8–17 Right herniotomy	0	Local
184721	33	F	Mild	2–21–17 Ligation left superior thyroid artery 3– 2–17 Ligation right superior thyroid artery 7–10–17 Thyroidectomy	0 0 0	Local Local Local
189767	53	F	Mild	4– 5–17 Amputation of left breast for cancer 4–21–17 Subtotal abdominal hysterectomy, appendectomy	0 0	Ether Ether
190768	59	M	Mild	4–19–17 Abdominal exploration, sarcoma mesentery	0	Ether
189925	48	M	Mild	4–21–17 Submucous resection	0	Local
191185	59	F	Mild	4–26–17 Cautery to cervix, polyp	0	None
192082	53	M	Mild	5– 8–17 Cholecystectomy, appendectomy	+	Ether
192580	51	F	Mild	5–12–17 Curettage, jaw, osteomyelitis	+	Ether
194296	50	M	Mild	5–19–17 Tonsillectomy	+	Local
192996	55	F	Moderately severe	5–29–17 Cholecystectomy	0	Ether
194400	62	M	Mild	5–21–17 Talma-Morison operation	0	Ether
194132	43	F	Mild	6– 5–17 Abdominal hysterectomy	0	Ether
200025	51	M	Mild	6– 6–17 Manipulation, shoulders	0	Ether
194569	54	F	Mild	6– 8–17 Cholecystectomy	0	Ether
196067	54	F	Mild	6– 9–17 Tonsillectomy	+	Local

* Patient died in hospital.

Table No. 1—(Continued)

Case	Age	Sex	Degree of diabetes	Operation	Sepsis	Anesthetic
197888	30	M	Moderately severe	6–16–17 Enucleation left eye	0	Local
133835	44	F	Mild	6–26–17 Subtotal abdominal hysterectomy 7– 9–17 Cholecystectomy	0 0	Ether Ether
196666*	20	M	Mild	6–29–17 Thyroidectomy	0	Ether
201643	44	F	Mild	8– 4–17 Thyroidectomy	0	Ether
204158*	46	M	Mild	8–13–17 Kraske, cancer of the rectum	0	Ether
209420	50	M	Mild	10–10–17 Amputation of right breast for cancer	0	Ether
214896	3	M	Severe	11–24–17 Drainage, submental abscess	+	Ether and local
210583	53	F	Mild	11–30–17 Thyroidectomy 11–27–18 Vaginal hysterectomy perineorrhaphy	0 0	Ether Ether
192303	59	F	Moderately severe	12–13–17 Perineorrhaphy	0	Ether'
216332	44	M	Mild	1– 2–18 Excision lipoma of neck	0	Ether
219323	57	M	Mild	2– 9–18 Cholecystogastrostomy, cancer of pancreas	0	Ether
221020	48	F	Mild	2–12–18 Splenectomy, spelnic anemia	+	Ether
223203	54	F	Moderately severe	3– 9–18 Vaginal hysterectomy	0	Ether
226214*	57	M	Mild	4–10–18 Suprapubic cystostomy	+	Local
226665	33	F	Mild	4–18–18 Appendectomy	0	Ether
227529	64	M	Mild	4–20–18 Amputation toe, gangrene	+	Local
230597	57	F	Moderately severe	6–14–18 Thyroidectomy	0	Ether
227684	54	F	Mild	6–19–18 Double cataract	0	Local
221951	56	M	Mild	7– 5–18 Herniotomy, inguinal	0	Ether
39692	41	F	Mild	7– 9–18 Thyroidectomy	0	Ether
236692	50	M	Mild	7–15–18 Cataract, right eye	0	Local
238199	62	F	Moderately severe	7–17–18 Drainage of abscess, toe	+	Local
225159	66	F	Mild	7–31–18 Cataract, right eye	0	Local
238868	53	F	Moderately severe	8– 7–18 Cholecystectomy 8–20–18 Excision portion of right breast	+ +	Ether Ether
243207	59	F	Mild	9– 2–18 Hysterectomy, fibroid	0	Ether
242720	23	F	Mild	9– 3–18 Cholecystectomy, appendectomy	+	Ether
244151	20	F	Mild	9–10–18 Dilatation and curettage	0	Ether
245930	57	F	Mild	9–25–18 Herniotomy, ventral hernia	0	Ether
248120	50	F	Moderately severe	10–23–18 Thyroidectomy	0	Ether
248296	69	M	Mild	11– 8–18 Cataract, right eye	0	Local
251508	57	F	Moderately severe	12– 5–18 Hysterectomy	0	Ether
253042	38	F	Mild	12–20–18 Cholecystectomy, appendectomy	+	Ether

* Patient died in hospital.

Table No. 1—(Continued)

Case	Age	Sex	Degree of diabetes	Operation	Sepsis	Anesthetic
254250	43	F	Mild	12–28–18 Hysterectomy, prolapse	0	Ether
256509*	62	M	Mild	2– 3–19 Permanent colostomy, cancer of rectum 2–10–19 Posterior excision, rectum	0 0	Ether Ether
259627	68	F	Mild	2–25–19 Subtotal hysterectomy, ovarian cyst	0	Ether
259876	33	F	Mild	3– 7–19 Perineorrhaphy	0	Ether
262002	69	M	Mild	3– 8–19 Suprapubic stab for bladder drainage 11–24–19 Prostatectomy, hypertrophy	0 0	Ether Ether
265477	54	F	Mild	4– 9–19 Vaginal hysterectomy	0	Ether
268038*	39	M	Mild	4–29–19 Herniotomy, umbilical hernia	0	Ether
269070	44	M	Mild	5– 7–19 Combined extraction, cataract, right eye	0	Local
268790	59	M	Mild	5–10–19 Division posterior root right gasserian ganglion	0	Ether
269194	57	F	Moderately severe	5–21–19 Vaginal hysterectomy.	0	Ether
271274	53	F	Mild	5–31–19 Thyroidectomy	0	Ether
274742	54	F	Mild	6–16–19 Extraction of teeth	+	Nitrous oxid
274621	64	M	Mild	6–26–19 Amputation penis, cancer	0	Local
201144	69	M	Mild	6–27–19 Amputation toe, gangrene	+	Local
276951	66	M	Mild	7–17–19 Circumcision	0	Local
282214	54	M	Mild	8– 7–19 Ligation left superior thyroid artery 8–13–19 Ligation right superior thyroid artery 12–16–19 Thyroidectomy	0 0 0	Local Local Ether
280168	54	F	Moderately severe	8–13–19 Thyroidectomy	0	Ether
238875	35	F	Mild	8–26–19 Vaginal hysterectomy, prolapse	0	Ether
285951	57	F	Mild	9–12–19 Thyroidectomy	0	Ether
288094*	58	F	Mild	10– 1–19 Thyroidectomy	0	Ether
288735	33	M	Mild	10– 1–19 Removal of stones of the pancreas, choledochotomy, removal of stones from common duct, cholecystostomy	0	Ether
287671	67	F	Moderately severe	10– 3–19 Amputation left breast for cancer	0	Ether
12578	48	F	Severe	10– 8–19 Combined extraction, cataract, right eye	0	Local
288864	44	F	Mild	10– 9–19 Thyroidectomy	0	Ether
247983	52	F	Mild	10–11–18 Combined extraction cataract, right eye 12– 4–19 First stage Mikulicz operation, cancer rectosigmoid	0 0	Local Ether
291313	36	M	Mild	10–14–19 Bilateral herniotomy	0	Ether
291868	51	F	Mild	10–23–19 Amputation left leg, gangrene	+	Ether

*Patient died in hospital.

Ether was administered 104 times; six of the deaths were among this group of patients, a mortality of 5.76 per cent; local anesthesia was used fifty-three times; two of the deaths were in this group of patients, a mortality of 3.77 per cent. Nitrous oxid was used only once. One operation of minor nature was performed without anesthesia. Joslin states that ether is a burden which may be easily borne by a mild diabetic, but may change a moderately severe to a severe case, and a severe case to a fatal case, and earnest attention should be given to this opinion. It is farthest from my purpose to advocate the general and indiscriminate use of ether on diabetic patients, and yet I venture to repeat a statement made in a former paper that even in the presence of diabetes ether given under proper conditions is the general anesthetic of choice. The experience of the anesthetist in giving general anesthesias, the degree and time of the anesthetic, and the workmanship of the operator play a great part in success or failure with this anesthetic. We have not used spinal anesthesia and our observation of its use elsewhere has not made us regretful. Gas oxygen also is not used generally by our surgeons. It is not satisfactory to the operator in abdominal cases, chiefly from the standpoint of relaxation and consistency of action. The French have made rather wide use of ethyl chlorid as a general anesthetic, administered by a mask, and Labbé mentions its special applicability to the diabetic. The administration of chloroform to the diabetic patient is hardly excusable. Local anesthesia, when applicable, carries its own recommendation.

Only eight patients in the series were classified as severe diabetics; twenty-three were moderately severe, and 103 were mild. Curiously enough all the deaths occurred in the mild cases. One patient who came merely for throat trouble in the course of a routine general examination was discovered to have diabetes. A tonsillectomy under local anesthetic was performed without the usual preoperative observation so that aside from the definite diagnosis no diabetic data is available. This patient died in coma forty-eight hours after the removal of the tonsils. Death occurred in six cases as the result of varied postoperative complications rather difficult to associate directly with diabetes. It might be conjectured that in the two pneumonia cases resistance to the infection was lowered by a preëxisting diabetes. The gas bacillus infection which occurred following a resection of carcinoma of the rectum seems to have been an accident unaffected by diabetes. The remaining three deaths are hardly open to discussion except from the standpoint of general surgical risk. With the exception of the death from tonsillectomy the deaths occurred in a group of cases in which the surgical risk would be appreciable without the presence of diabetes (Table 2).

TABLE NO. 2
Diabetic deaths in the hospital

Case	Age	Sex	Operation	Cause of Death	Anesthetic	Days after operation	Degree of diabetes	Sepsis	Associated Condition	Necropsy
176239	55	F	Thyroidectomy	Bronchopneumonia	Ether	3	Mild	0	Thyroid toxemia, myocarditis	+
196666	20	M	Thyroidectomy	Bronchopneumonia and myocarditis	Ether	2	Mild	0	Thyroid toxemia, myocarditis	+
204158	46	M	One stage Kraske for carcinoma of rectum	Diabetic coma	Ether	4	Mild	0	0	0
160174	29	M	Tonsillectomy	Diabetic coma	Local	2	Mild	+	Multiple sclerosis	+
226214	57	M	Suprapubic Cystostomy	Pyelonephritis	Local	52	Mild	+	Prostatic bladder retention, marked cystitis, low kidney function	+
268038	39	M	Umbilical herniotomy	Bilateral pulmonary fat embolism	Ether	6	Mild	0	Marked obesity	0
256509	62	M	Permanent colostomy and posterior excision of rectum and anus for cancer of rectum	Gas bacillus septicemia	Ether	28	Mild	0	Moderate cachexia	0
288094	58	F	Thyroidectomy	Bronchopneumonia	Ether	5	Mild	0	Thyroid toxemia	+

If a detailed classification of the surgical conditions found in diabetic patients is attempted it may become rather complex. We find various and not necessarily conflicting ideas in the literature. Falta describes surgical conditions which tend to or already do bear a relationship to diabetes and those which do not. As a simple broad classification from one view point this has an attraction. His description of the first group carries no implication relative to the cause of diabetes, but catalogs these surgical diseases as potential influences on diabetes. I should include in the first group all infectious conditions, including furuncle, carbuncle and gangrene, mentioned by him, and all definite affections of the gallbladder, bile passages or pancreas, and diseases of the thyroid. Our series included fourteen cholecystectomies, one cholecystostomy, one cholecystogastro-enterostomy for carcinoma of the pancreas, and one choledochotomy for stones in the common duct and pancreas. Our general impression has been that following a successful operation for conditions such as these just described the tendency has been toward improvement of the diabetes. It is also of interest to note that twenty-five patients of the series were operated on for diseases of the thyroid. Eight had exophthalmic goiters and seventeen had adenomas of the thyroid. Another grouping which appeals to me as rather essential divides the surgical conditions into the vital and the nonvital, with absolutely no relation to major or minor surgery. The first group comprises those conditions threatening the life or fundamental health of the patient immediately or ultimately. Strouse mentions a classification of the emergency and non-emergency operations. This is rather important from the standpoint of its relation to preoperative treatment. I believe with Strouse and Fitz that delay may prove dangerous in acute infection, and if the infection is definitely shown seriously to disturb metabolism preoperative dietary measures are often unavailing and in fact add to the surgical risk.

In which diabetic patients do we expect the greatest hazard? Our mortality in operations on infected tissue was 8 per cent, and on noninfected tissue 4 per cent. Such conditions as nephritis, arteriosclerosis, old age, and obesity will contribute to the surgical hazard in proportion to their degree. To these may be added cardiac and circulatory diseases, debilitation from any cause, and the gravity of the surgical situation itself although unattended by any complication.

The majority of our diabetic patients coming to operation had the disease in a mild form, that is, their tolerance under a few days' management is shown to be 80 gm. or higher. Our first purpose in the preoperative treatment is to make careful investigation for associated conditions and complications, especially infections and renal disturbances, and second to render the urine free from sugar as rapidly as possible, establish tolerance roughly, bring the diet back to a maintenance caloric value and be sure the patient is free from acidosis. The details of this procedure in general are common knowledge; we are closely following the Joslin methods. Special attention is given to the number of days of starvation necessary to clear the urine of sugar, as well as the general effect on the patient of radical manipulation of the diet. Patients whose urine clears slowly and who complain of marked weakness and other distressing symptoms while starving are, if circumstances permit, carried on medical treatment for several weeks before being sent to the operating room.

We frequently are able to bring a patient to a satisfactory maintenance diet without reaching his carbohydrate tolerance. These patients may be saved considerable time as it is not necessary to drop back to a low diet and again bring it up. The maintenance diet is kept up for several days, probably averaging about a week, after which, other things being satisfactory, the patient is transferred directly to the operating room. There is no fixed time limit to any part of the preoperative treatment, and the question of time is largely dependent on the aspect in the individual case.

Our requirements of the diabetic patient before operation are not new or different. We wish his urine to be free of sugar and that he show no sign of acidosis after he has been for several days (from five to seven) on a diet very low in fat and containing a sufficient caloric value to supply his needs while he is at rest. This requirement is not entirely an arithmetic calculation. I have seen diabetics who require at the least thirty calories to the kilo of weight, and I have had a moderately severe diabetic on half day and at times full day orderly duty for weeks on a diet which did not quite supply fifteen calories to the kilo. He maintained his nutrition and was fairly comfortable although he complained of weakness and slight dizziness.

Our routine urinalysis, aside from the ordinary tests, consists in the quantitative and qualitative analysis for sugar, the ferric chlorid test for diacetic acid, and the estimation of the total quantity of ammonia in the twenty-four hour specimen. A patient who excretes more than 1.5 gm. of ammonia, or shows a positive ferric chlorid reaction, should have more prolonged treatment. During the past year we have used routinely also the determination of the carbon dioxid of the blood plasma as an index to acidosis. Foster has stated that blood sugar is the index to diabetes. Although we have been determining the percentage of blood sugar for several years we have found it of especial value only in a very few cases in which we discovered that the blood sugar remained persistently high after the urine had become sugar free. We have not looked with favor on this type of patient as a surgical risk although one recent patient, not in the series reported, was dieted with the blood sugar as the sole index, and finally had an amputation of the leg for gangrene. This woman had a previous history of diabetes; our tests showed no sugar in the urine but 0.3 per cent of sugar in the blood. There was some evidence of a kidney lesion but her kidney function was proved to be good. She passed safely through the operation.

In my former paper I mentioned our routine use of sodium bicarbonate, but for at least three years we have not used sodium bicarbonate for our surgical diabetics and, in all candidness, we see absolutely no consequent difference in the behavior of these patients during operation or in their postoperative convalescence. This about-face in our practice was due to Joslin's opinion that large doses of sodium bicarbonate are frequently detrimental to patients with threatened coma. Our great ally is fluid, by mouth, by rectum, and subcutaneously or intravenously, but fluid in some form immediately the patient leaves the operating table and pushed until the end of forty-eight hours or longer if thought necessary. All patients with signs of acidosis or threatened coma should receive 1000 c.c. of fluid during every six hours. For the first day or two orange juice up to 250 c.c. or 300 c.c. a day has prove a very acceptable and satisfactory form of food. We have found it beneficial as a source of carbohydrate to patients who have a tendency to acidosis. This has been especially true in young children who have reacted rather unfavorably to starvation longer than forty-eight hours. From this point on our postoperative treatment has not differed greatly from our preoperative. Tolerance is again established and the patient is placed on a strictly medical regime which has for its object the education of the patient to a point where he may assume the responsibility of his future treatment.

Answers to questionnaires have been received from seventy-six of the 126 patients who recovered from operation and returned home. These replies were written from six months to five years following operation. Twenty-two patients died within an average of eighteen months after operation; six of these are reported to have died of diabetes, the remainder from various causes, several during the influenza epidemics. Forty-six of the remaining fifty-four patients consider themselves cured of the condition for which they were operated on, six are considerably improved, and two report no improvement. All but three or four are continuing more or less successful efforts at dieting, their successes depending a great deal on the circumstances in which they are obliged to live.

CONCLUSIONS

One hundred fifty-nine operations of all kinds have been performed in the Clinic on diabetic patients with a mortality of 5.03 per cent. Ether was administered 104 times, with a mortality of 5.76 per cent. The mortality in operations on infected tissue was twice as great as on uninfected tissue, and, judging from the literature, this is the usual ratio. Sixty-eight per cent of the seventy-six patients operated on, from whom we have heard, have obtained relief from various crippling, health destroying and life menacing conditions from which they were suffering aside from their diabetes.

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IV

CIRCULATORY ORGANS

OBSERVATIONS ON NEGATIVITY OF THE FINAL VENTRICULAR T WAVE OF THE ELECTROCARDIOGRAM*

FREDRICK A. WILLIUS

A review of the literature on electrocardiography, both experimental and clinical, at once reveals a variance in views as to the interpretation of the normal electrocardiogram. The two views that have gained broadest recognition are: (1) All waves are manifestations of excitation and contraction of heart muscle, and (2) the waves result from electric changes accompanying conduction of the impulse and contraction of the muscle.

Einthoven assumed that the right ventricle represents the cardiac base and the left ventricle the apex, and that the dominance of negativity in the right ventricle causes an upward deflection, while dominance in the left causes a downward deflection of the galvanometer. Thus the R wave is ascribed to contraction of the right heart, the S wave to contraction of the left heart, and the horizontal S-T interval to neutralization of basal and apical negativity. The T wave represents contraction of the right ventricular base outlasting that of the left.

Eppinger and Rothberger object to Einthoven's assumption in ascribing the rôle of cardiac base to the relatively weak right ventricle and regarding the left ventricle with its massive muscle bulk as the apex.

The views of Kraus and Nicolai are based on the structural arrangement of the ventricular musculature into systems. Following auricular contraction the impulse passes through the auriculoventricular bundle and its contiguous structures. The long P-R interval is explained by slow conduction and the absence of appreciable action currents at this time due to the small muscle mass. The R wave is ascribed to primary activity of the basal portions of the papillary muscles. As the excitation wave spreads toward the apex the termination of the R wave occurs. The S-T interval is explained by the absence of potential between base and apex. The T wave results from late return of negativity to the base.

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The views of Einthoven, Kraus and Nicolai agree in general in emphasizing the antagonistic action of electric potential between base and apex.

In distinct opposition to the views already expressed, Hoffmann concluded that the electrocardiogram results from two actions, impulse conduction, and muscle contraction. The Q R S complex results from passage of the impulse through the ventricular conduction system and the S-T interval and the T wave from electric potential caused by the contracting ventricle. Hoffmann produced standstill of the frog heart by the application of muscarin, obtained simultaneous electrocardiographic and ventriclar suspension curves, and found that the electrocardiogram of the nonbeating heart differs from the normal only in the absence of the T wave. When the muscarin effect was abolished by atropin and the beats returned the T wave reappeared.

Eyster and Meek, as a result of their experimental work on the relation of the line of isopotential to the formation of the electrocardiogram, and their critical review of the literature, in general agree with Hoffmann's theory. They believe the R wave to be concerned with conduction, but they do not ascribe definite structures as conducting mediums. The T wave is the expression of preponderance of contraction on one side of the line of equipotential. Eyster and Meek further show the differences between physiologic curves of conduction and contraction. When a nerve is stimulated where conduction alone occurs, a single monophasic or diphasic electric response occurs. In skeletal muscle this rapid electric change is followed by a slower and more prolonged electric variation. This conforms with the general contour of the electrocardiographic deflections; the R wave is abrupt and steep, the T wave blunt and prolonged.

CARDIAC EVENTS AND THE ELECTROCARDIOGRAM

The relationship of the waves of the electrocardiogram to definitely known cardiac events strongly supports the "conduction-contraction" theory. By a consideration of accepted relationships of the normal heart sounds a working basis for comparison is established.

Einthoven, Flohil and Battaerd have shown that the first sound begins at the initiation of ventricular systole and lasts from 0.07 to 0.10 second, is followed by a pause varying from 0.15 to 0.25 second, and then succeeded by the second sound. These observations have been confirmed by other investigators.[1, 10, 35] The second sound follows closely on the closure of the semilunar valves,[37] begins simultaneously with the rise of intraventricular pressure,[14] and gains its maximum amplitude during this period.[33] That the second sound is an early diastolic event has been shown clearly.[26, 36]

Kahn has demonstrated that the first sound falls in the pause between the R and the T waves and begins at the moment the R wave disappears and a short time before the rise of the T wave. The second sound begins 0.05 second after the end of the T wave. This relationship reveals the fact that the R wave is completed before ventricular contraction begins and indicates conduction rather than contraction. The T wave definitely occupies the period associated with actual ventricular contraction.

In clinical studies of the abnormalities of the Q R S group they are largely ascribed to disease of the ventricular conduction system.[1, 24, 34, 38, 39] It must be recognized, however, that the graphic representation of contraction in the electrocardiogram is the expression of changes in electric potential and not the translation of actual contraction. The iso-electric portion of the intervals S-T and a portion of T-P are not latent in the sense of a refractory phase.

CONSIDERATION OF ELECTROPOTENTIAL

Waller and Reid demonstrated a line of equipotential passing through the heart from base to apex in relation to any two derivations from the extremities. A preponderance of negativity above this line, representing the cardiac base, caused deflection of the galvanometer connected to both upper extremities in a manner to indicate relative negativity of the electrode connected with the right arm. The arm becomes relatively negative in derivations from an arm and a leg. Dominance of negativity below the equipotential line deflects the galvanometer in the opposite direction.

HYPOTHESIS OF T WAVE NEGATIVITY

The three derivations of the electrocardiogram possess symbols of definite electropotential in relation to their electrodes. In the normal electrocardiogram Derivation I bears symbols as follows: right arm −, left arm +; Derivation II, right arm −, left leg +; and Derivation III, left arm −, left leg + (Fig. 112). This arrangement implies positive or upright deflections in all derivations of the electrocardiogram. If it is assumed that the "conduction-contraction" theory is correct the T wave is the expression of preponderance of contraction on one side of the line of equipotential. T wave negativity (inverted) therefore results from changes in contraction preponderance. The negativity of this wave in certain isolated or combined derivations of the electrocardiogram is indicative of definite potential changes affecting contraction proponderance in various regions of the cardiac musculature.

In the normal heart, therefore, according to standard derivations, the T wave in all derivations is positive (upright), the right upper zone of potential is strongly electronegative to the apical zone while the left upper zone is iso-electric. This potential arrangement is illustrated in Figure 112.

For reasons of simplification I have represented the three derivations by the sides of an equilateral triangle. To prevent misunderstanding it should be stated that the schematic figure employed, divided into zones of electropotential, is not based on mathematic consideration. The right upper zone in general corresponds to the sinus region of the heart and in the normal potential arrangement, is electronegative.

Confirmation of this is found in the researches of Keith and Flack, Wybauw, Lewis, Oppenheimer and Oppenheimer, Brandenburg and Hoffmann, and Ganter and Zahn, who have shown that the cardiac impulse takes its origin in a collection of specialized tissues, a remnant of the primordial sinus. This structure lies in the sulcus terminalis at the juncture of the superior vena cava and the right auricular appendage, and is the seat of primary cardiac negativity.

Changes in the normal potential distribution produce T wave negativity in isolated or combined derivations of the electrocardiogram. Reversal of potential in one derivation alters cardiac potential so that T wave negativity in that derivation occurs.

T WAVE NEGATIVITY

Many opinions have been expressed as to the significance of negativity or inversion of the T wave in isolated or combined derivations of the electrocardiogram.

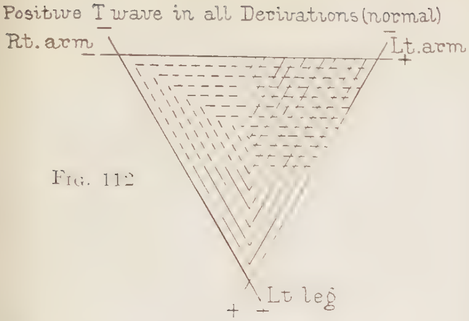

FIG. 112

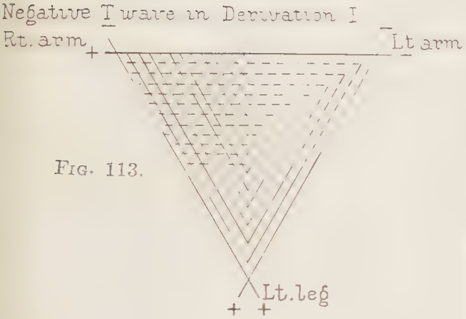

FIG. 113.

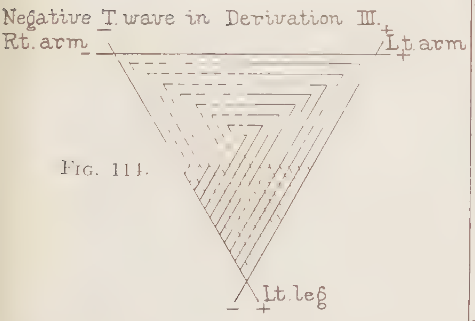

FIG. 114.

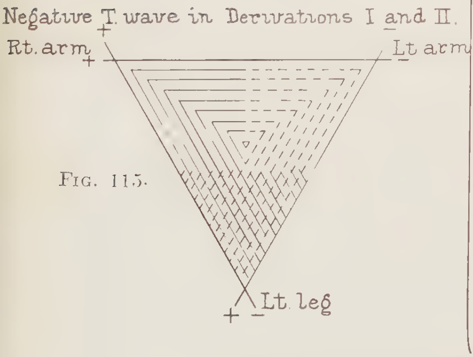

FIG. 115.

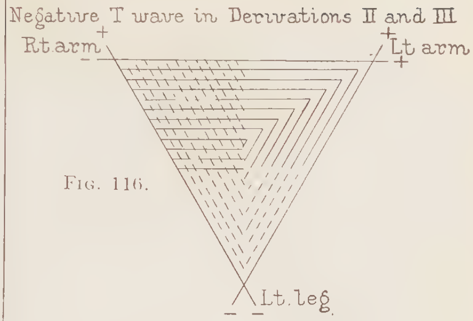

FIG. 116.

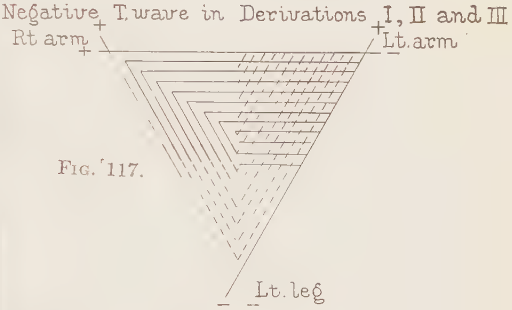

FIG. 117.

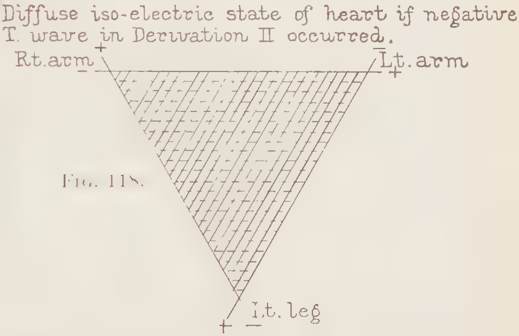
Diffuse iso-electric state of heart if negative T. wave in Derivation II occurred.
Rt. arm
+
−
Lt. arm
−
+
Lt. leg
+
−

FIG. 118.

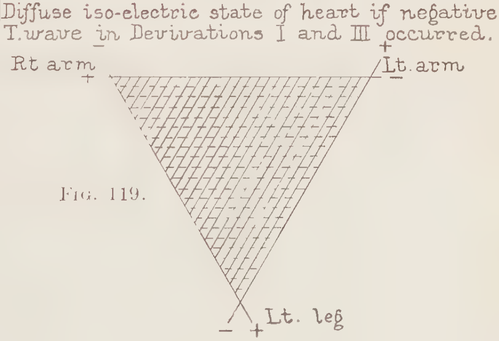
Diffuse iso-electric state of heart if negative T. wave in Derivations I and III occurred.
Rt. arm
+
Lt. arm
+
−
Lt. leg
−
+

FIG. 119.

FIGS. 112–119.—Observations on negativity of the final ventricular T wave of the electrocardiogram.

The effect of digitalis on the heart as manifested by negativity of the T wave is well known;[4] it has been ascribed to muscular ventricular redistribution or possibly to alteration in muscular contractility. These changes are not permanent.

Numerous statements may be found in which myocardial damage is ascribed to T wave negativity in certain derivations [3, 18, 19, 25] and again these occurrences have been noted in apparently normal hearts [13, 20, 31], affecting largely Derivation III.

Smith, during his experimental work on coronary ligations, observed interesting changes in the T wave. The most constant changes in the electrocardiogram following ligation of any branch of the left coronary artery affected the T wave. A strongly positive to a markedly negative wave resulted fairly constantly with a slower return to positive or iso-electric. The negativity was usually observed within twenty-four hours after ligation and lasted for from three to four days. The duration seemed to bear a relationship to the size of the artery ligated. This work offers a tangible basis in directing attention to changes in the intrinsic blood supply of the heart, as evidenced by greater or lesser derangements of cardiac function. Morison has shown that blood volume alterations may produce changes detectable in the electrocardiogram.

Increased general cellular function implies increased blood volume for the maintenance of normal tissue metabolism. In a specialized organ this augmentation is manifested by an increase in its function. In the heart increase in the blood volume beyond physiologic limits increases contraction. I refer particularly to increase of ventricular blood volume since coronary volume is largely dependent on this factor. Because of impairment or disease of certain intrinsic channels of blood supply the affected muscle does not receive the requisite amount of blood properly to maintain function while the unaffected muscle demands greater blood volume for relatively more efficient contraction. This is an explanation for T wave changes in isolated or combined derivations occurring permanently or temporarily.

THE ACTION OF THE CARDIAC NERVES ON T WAVE NEGATIVITY

Stimulation of the cardiac vagus has been shown to produce negativity of the T wave, [5, 29] and the same observation is noted following stimulation of the left cervical sympathetic branches.[28]

A series of clinical observations were conducted on patients having negative T waves in isolated or combined derivations of their electrocardiograms. Following the initial tracing, pressure was applied in turn to the right vagus region in the neck, to the left vagus region, and finally to the right eyeball (oculocardiac reflex) and the respective electrocardiograms obtained. In no instance was any change noted in the negative T wave or in the positive T wave of the unaffected derivations. Atropin (gr. $^{1}{}_{150}$) was then administered subcutaneously and records obtained every ten minutes for forty minutes. Again no effect on the T wave was noted. No change occurred following the subcutaneous administration of adrenalin (0.5 c.c. of a 1 to 1000 solution). These clinical procedures, however, are obviously not so accurate as direct experimental stimulation.

The present status of cardiac histopathology fails to explain many derangements of function. Histologic studies do not indicate why auricular fibrillation occurs in one heart and auricular flutter in another. Disease of the cardiac conduction system is more definite histologically. Involvement below the auriculoventricular bundle is often associated with unquestionable intrinsic vascular changes.

There has been no adequate explanation of the occurrence of the negative T wave in isolated or combined derivations of the electrocardiogram. In the Mayo Clinic we have repeatedly observed the negative T wave in Derivation I, in Derivation III, in combined Derivations I and II, in combined Derivations II and III, and in combined Derivations I, II, and III. No instances of negativity in Derivation II or in combined Derivations I and III are recorded. This observation in 7,000 electrocardiographic examinations eliminates the element of coincidence. There is a definite reason why these changes do not occur. Lewis states that the T wave is always upright in Derivation II alone.

T wave negativity in Derivation I, Figure 113.—Figure 113 represents the arrangement of potential existing with this abnormality. The left arm becomes electronegative to the right while the other signs remain unchanged. The right upper zone, instead of being electronegative, becomes iso-electric while the left upper becomes electronegative to the apex. The occurrence of an iso-electric state in the right upper zone is a marked departure from the normal in that the area of primary electronegativity is altered.

T wave negativity in Derivation III, Figure 114.—The left leg becomes electronegative to the left arm; the other derivations remain unchanged. The right upper zone remains electronegative with reference to the left upper. The apical zone becomes iso-electric. This distribution is but a slight deviation from normal, in that the right upper zone remains electronegative.

T wave negativity in combined Derivations I and II, Figure 115.—The left arm becomes electronegative to the right arm and the left leg electronegative to the right arm. The third derivation remains unchanged. The left upper zone becomes electronegative to the right, and the apical zone becomes iso-electric. This arrangement again deviates from the normal in altering the area of primary electronegativity; it is a lesser change in that the right upper zone becomes electropositive instead of iso-electric.

T wave negativity in combined Derivations II and III, Figure 116.—The left leg becomes electronegative to both arms. Derivation I remains unchanged. The apical zone becomes electronegative to the left upper while the right upper zone becomes iso-electric. This arrangement as in Derivation I is a marked change from normal, in that the area of primary electronegativity becomes iso-electric.

T wave negativity in combined Derivations I, II, and III, Figure 117.—All derivations reverse their signs in relation to each other. The apical zone becomes electronegative to the right upper while the left upper zone becomes iso-electric. The upper zones assume just the opposite relationship to each other that occurs in combined Derivations II and III. Here again the potential distribution is disturbed, the area of primary electronegativity becoming electropositive, approaching the changes accompanying T wave negativity in combined Derivations I and II.

Figures 118 and 119 illustrate the reasons why T wave negativity in Derivation II and in combined Derivations I and III does not occur. In Derivation II the left leg would be electronegative to the right arm while the other derivations would remain unchanged. This distribution would imply a diffuse iso-electric cardiac state and would indicate that cardiac contraction had ceased. In combined Derivations I and III the left arm would be electronegative to the right and the left leg to the left arm. This arrangement likewise would indicate a diffuse iso-electric state.

The greater the deviation from the normal potential distribution the greater the significance of the disorder responsible for the change. The greatest change occurring which is compatible with life is the iso-electric state occupying the right upper zone. Therefore T wave negativity in Derivation I and in combined Derivations II and III should be associated generally with grave heart disease. Next in significance should be those distributions of potential rendering the left upper zone electronegative to the right and represented by T wave negativity in combined Derivations I and II and in combined Derivations I, II, and III.

In the distribution which most closely approximates normal the T wave is negative in Derivation III. In these cases the normal potential relationship of the right upper zone is maintained.

CLINICAL CONSIDERATION OF T WAVE NEGATIVITY

This study comprises 1106 cases of T wave negativity in the electrocardiograms. One hundred forty instances (12.6 per cent) were noted in Derivation I, 688 (62.2 per cent) in Derivation III, 62 (5.6 per cent) in combined Derivations I and II, 171 (15.5 per cent) in combined Derivations II and III, and 45 (4.1 per cent) in combined Derivations I, II, and III. There was no instance of T wave negativity in Derivation II nor in combined Derivations I and III. Patients who had had digitalis within six weeks of the time of electrocardiographic examination were not included in this series.

T WAVE NEGATIVITY AND VENTRICULAR PREPONDERANCE

In the complete series about half (46.6 per cent) of the electrocardiograms were associated with preponderance of the left ventricle. Preponderance of the right ventricle is evidenced by a negative R wave in Derivation I and by a positive R wave in Derivation III. In cases of preponderance of the left ventricle these changes are reversed. Right preponderance was infrequent (17.3 per cent) and no unbalance was present in 36.1 per cent of the electrocardiograms. Preponderance of the left ventricle occurred most often associated with T wave negativity in Derivation I and in combined Derivations I and II. No instance of right preponderance was noted with negativity in combined Derivations I, II, and III. These observations are summarized in Table 1.

TABLE 1.—T WAVE NEGATIVITY AND VENTRICULAR PREPONDERANCE

	Total	Left preponderance	Percentage	Right preponderance	Percentage	None	Percentage
Derivation I	140	120	85.7	5	3.6	15	10.7
Derivation III	688	274	39.8	132	19.2	282	41.0
Derivations I and II	62	52	83.9	4	6.4	6	9.7
Derivations II and III	171	43	25.2	51	29.8	77	45.0
Derivations I, II and III	45	27	60.0	0	0	18	40.0
Total	1106	516	46.6	192	17.3	398	36.1

TABLE 2.—GRAVE HEART DISEASE ASSOCIATED WITH T WAVE NEGATIVITY

	Total	Arborization block	Delayed auriculo-ventricular conduction	Complete auriculo-ventricular dissociation	Auricular fibrillation	Auricular flutter	Ventricular tachycardia	Aortic disease	Angina pectoris
Derivation I	140	53	3	3	19	1	1	16	9
Derivation III	688	3	2	0	11	0	0	8	21
Derivations I and II	62	14	2	0	5	0	1	6	1
Derivations II and III	171	11	3	1	24	0	1	13	3
Derivations I, II and III	45	3	3	0	11	0	0	8	2
Total	1106	84	13	4	70	1	3	51	36

ASSOCIATED DISEASES

T wave negativity in Derivation I (140 *cases*).—Myocardial degeneration associated with the hypertension group occurred with greatest frequency (38.6 per cent) in the patients having T wave negativity in Derivation I of their electrocardiograms. Three factors are probably responsible for the myocardial changes accompanying hypertension: (1) The cause or causes primarily responsible for the constitutional disorder; (2) the action on the myocardium of the retention products or of the intermediate products of incomplete metabolism or toxic agents resulting from imperfect renal or tissue function, and (3) the increased cardiac work, affecting largely the myocardium, resulting from the hypertension *per se* and the alterations in cardiovascular balance.

Chronic endocarditis occurred second in order of frequency (22.1 per cent of the cases). The myocardial damage attending this disorder occurs concomitant with or secondary to the endocardial invasion (Table 3). In no instance was the cardiac examination negatve. In the majority of instances grave heart disease was present.

Fifty-three patients had arborization block, three had delayed auriculoventricular conduction, three had complete auriculoventricular dissociation, nineteen had auricular fibrillation, one had auricular flutter and one had ventricular tachycardia. Sixteen patients had aortic disease. Nine had angina pectoris.

The high incidence of grave heart disease in this group verifies my previous statement regarding the potential distribution responsible for this negativity as being the greatest departure from normal. The right upper zone is iso-electric instead of electronegative.

Table 3.—Associated Diseases

T wave negativity in Derivation I

		Degenerative processes			Infections			Local nutritional disturbances				
Decade	Total	Hypertension with and without clinical nephritis	Exophthalmic goiter	Adenomas with hyperthyroidism	Chronic endocarditis	Chronic myocarditis	Syphilis	Arteriosclerosis	Angina pectoris	Congenital heart disease	No cardiac findings	Inconclusive cardiac findings
11–20	2	0	0	0	2	0	0	0	0	0	0	0
21–30	5	0	0	0	4	1	0	0	0	0	0	0
31–40	7	1	0	0	3	2	0	0	0	0	0	1
41–50	28	10	2	2	7	1	5	1	1	0	0	0
51–60	40	16	1	2	6	6	2	7	4	0	0	0
61–70	54	25	0	2	9	7	0	11	4	0	0	0
71–80	4	2	0	0	0	2	0	0	0	0	0	0
Total.....	140	54	3	6	31	19	7	19	9	0	0	1
Per cent.			45.0			40.7		13.6				0.7

T wave negativity in Derivation III (*688 cases*).—The relative frequency of T wave negativity occurring in Derivation III is at once apparent.

The myocardial degeneration secondary to exophthalmic goiter was the most frequently associated condition (19.2 per cent). Myocardial damage due to exophthalmic goiter involves the cellular action of thyroxin[17] (thyroid active principle) on the myocardium,[27] and the increased cardiac work accompanying the rise of the basal metabolic rate.

Chronic endocarditis occurred in 16.9 per cent and chronic myocarditis in 14.8 per cent. By chronic myocarditis I refer to those cases of inflammatory origin in contradistinction to the cases of myocardial degeneration. Myocardial degeneration associated with the hypertension group occurred in only 10.8 per cent of cases (Table 4).

Grave heart disease is relatively infrequent in this group; 3 patients had arborization block, 2 had delayed auriculoventricular conduction, and 11 auricular fibrillation. Eight patients had aortic disease and 21 had angina pectoris. Twenty per cent of the patients had no demonstrable evidence of organic heart disease. Of this number 40 per cent had cardiac neurosis.

TABLE 4.—ASSOCIATED DISEASES

T wave negativity in Derivation III

		Degenerative processes			Infections			Local nutritional disturbances				
Decade	Total	Hypertension with and without clinical nephritis	Exophthalmic goiter	Adenomas with hyperthyroidism	Chronic endocarditis	Chronic myocarditis	Syphilis	Arteriosclerosis	Angina pectoris	Congenital heart disease	No cardiac findings	Inconclusive cardiac findings
1–10	10	0	0	0	4	0	0	0	0	4	0	2
11–20	62	2	20	0	13	2	1	0	0	0	22	2
21–30	190	6	55	3	40	19	2	0	0	1	46	18
31–40	161	12	39	5	32	15	6	0	0	0	35	17
41–50	138	28	16	5	18	25	5	4	4	1	19	17
51–60	83	21	2	9	5	27	5	7	6	0	1	6
61–70	39	4	0	2	4	12	0	12	10	0	2	3
71–80	5	1	0	0	0	2	0	2	1	0	0	0
Total.....	688	74	132	24	116	102	19	25	21	6	125	65
Per cent....		33.4			34.4			3.7		0.9	18.2	9.4

The relative infrequency of grave heart disease and the high percentage of apparently normal hearts in this group are in marked contrast to the findings associated with T wave negativity in Derivation I. These findings are in accord with the hypothetical significance of T wave negativity in Derivation III. The potential distribution in this T wave negativity is illustrated in Figure 114. The right upper zone remains electronegative, the other zones reverse their potential, establishing an arrangement which does not materially depart from the normal.

The potential distribution occurring in such a relatively high percentage of apparently normal hearts and the frequent transient T wave negativity in Derivation III make functional myocardial fatigue a causative possibility in a certain number of cases at least.

T wave negativity in combined Derivations I and II (62 *cases*).—Myocardial degeneration associated with the hypertension group occurred in half (50 per cent) of the patients having T wave negativity in combined Derivations I and II. Chronic endocarditis was present in 20.9 per cent of the cases. In no instance was the cardiac examination negative. These findings are summarized in Table 5.

TABLE 5.—ASSOCIATED DISEASES

T wave negativity in Derivations I and II

		Degenerative processes			Infections			Local nutritional disturbances				
Decade	Total	Hypertension with and without clinical nephritis	Exophthalmic goiter	Adenomas with hyperthyroidism	Chronic endocarditis	Chronic myocarditis	Syphilis	Arteriosclerosis	Angina pectoris	Congenital heart disease	No cardiac findings	Inconclusive cardiac findings
21–30	7	0	0	0	6	1	0	0	0	0	0	0
31–40	5	3	0	0	2	0	0	0	0	0	0	0
41–50	13	7	0	1	1	3	0	0	0	0	0	1
51–60	20	14	1	0	2	1	1	1	1	0	0	0
61–70	15	7	0	1	2	1	1	3	0	0	0	0
71–80	2	0	0	0	0	1	0	1	0	0	0	0
Total.....	62	31	1	2	13	7	2	5	1	0	0	1
Per cent....		54.8			35.5			8.1				1.6

About half (46.7 per cent) of the cases were associated with grave heart disease. Fourteen patients had arborization block, 2 had delayed auriculoventricular conduction, 5 had auricular fibrillation, and 1 had ventricular tachycardia. Six patients had aortic disease and one of these, had an aortic aneurysm. One patient had angina pectoris.

Reference to the potential distribution responsible for T wave negativity in this derivation combination (Fig. 115) shows that the normal potential (electronegativity) of the right upper zone is disturbed. The left upper zone becomes electronegative to the right upper. Although this is a distinct departure from normal, it is less marked than those states in which the right upper zone becomes isoelectric.

T wave negativity in combined Derivations II and III (171 *cases*).—Chronic endocarditis occurred with greatest frequency (26.9 per cent) in those patients having T wave negativity in combined Derivations II and III. In order of frequency followed myocardial degeneration associated with exophthalmic goiter (21.0 per cent), chronic myocarditis (17.5 per cent), and myocardial degeneration associated with the hypertension group (15.8 per cent).

A large percentage of the patients had grave heart disease. Eleven patients had arborization block, three had delayed auriculoventricular conduction, one had complete auriculoventricular dissociation, 24 had auricular fibrillation, and one ventricular tachycardia. Thirteen patients had aortic disease and three had angina pectoris. In nine cases the cardiac examination was negative. These observations are illustrated in Table 6.

Again the reader is referred to Figure 116, which illustrates the potential distribution in T wave negativity in this derivation combination. The similarity to the potential arrangement attending T wave negativity in Derivation 1 may be noted.

T wave negativity in combined Derivations I, II, and III (45 *cases*).—T wave negativity in Derivations I, II, and III constituted the smallest group, comprising only 4.1 per cent of the total series.

Myocardial degeneration associated with the hypertension group occurred most often (35.5 per cent) and in order of occurrence chronic endocarditis (24.4 per cent) and chronic myocarditis (20.0 per cent). Every patient in this group had definite clinical evidence of heart disease (Table 7).

Three of the patients with the graver forms of heart disease had arborization block, three delayed auriculoventricular conduction, and eleven auricular fibrillation. Eight patients had aortic disease and two had angina pectoris. If the potential distribution in this disorder is taken into consideration the apical zone will be found electronegative to the right upper, while the left upper zone will be iso-electric (Fig. 117). This arrangement is similar to that attending T wave negativity in combined Derivations I and II in that the right upper zone is electropositive. It likewise is a distinct deviation from normal.

Table 6.—Associated Diseases

T wave negativity in Derivations II and III

		Degenerative processes			Infections			Local nutritional disturbances				
Decade	Total	Hypertension with and without clinical nephritis	Exophthalmic goiter	Adenomas with hyperthyroidism	Chronic endocarditis	Chronic myocarditis	Syphilis	Arteriosclerosis	Angina pectoris	Congenital heart disease	No cardiac findings	Inconclusive cardiac findings
11–20	12	1	4	0	5	2	0	0	0	0	0	0
21–30	45	1	13	1	16	6	1	0	0	1	3	3
31–40	39	4	10	0	14	4	0	0	0	0	5	2
41–50	34	5	8	3	6	8	1	0	0	2	1	0
51–60	28	10	0	1	4	8	0	4	2	0	0	1
61–70	12	5	1	0	1	2	1	2	1	0	0	0
71–80	1	1	0	0	0	0	0	0	0	0	0	0
Total......	171	27	36	5	46	30	3	6	3	3	9	6
Per cent.....			39.8			46.2		3.5		1.7	5.3	3.5

Table 7.—Associated Diseases

T wave negativity in Derivations I, II, and III

		Degenerative processes			Infections			Local nutritional disturbance				
Decade	Total	Hypertension with and without clinical nephritis	Exophthalmic goiter	Adenomas with hyperthyroidism	Chronic endocarditis	Chronic myocarditis	Syphilis	Arteriosclerosis	Angina pectoris	Congenital heart disease	No cardiac findings	Inconclusive cardiac findings
11–20	1	0	0	0	1	0	0	0	0	0	0	0
21–30	4	0	0	0	2	1	0	0	0	1	0	0
31–40	7	1	0	0	4	1	1	0	0	0	0	0
41–50	9	2	1	2	0	3	1	0	0	0	0	0
51–60	12	8	0	0	2	0	0	2	1	0	0	0
61–70	12	5	0	0	2	4	0	1	1	0	0	0
Total......	45	16	1	2	11	9	2	3	2	1	0	0
Per cent.....			42.2			48.8		6.6		2.2		

TABLE 8.—ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH T WAVE NEGATIVITY

	Total	T wave negativity unattended	Sinus arhythmia	Auricular premature contractions	Auricular and nodal premature contractions	Auricular and ventricular premature contractions	Nodal premature contractions	Nodal premature contractions and sinus arhythmia	Ventricular premature contractions	Ventricular and nodal premature contractions	Ventricular premature contractions and sinus arhythmia	Auricular fibrillation	Auricular fibrillation and ventricular premature contractions	Auricular fibrillation and aberrant Q R S complexes in isolated derivations	Auricular fibrillation and aberrant Q R S complexes in isolated derivations and ventricular premature contractions	Arborization block	Arborization block and auricular premature contractions	Arborization block and ventricular premature contractions	Arborization block and auricular fibrillation	Arborization block and delayed auriculo-ventricular conduction	Aberrant Q R S complexes in isolated derivations	Aberrant Q R S complexes in isolated derivations and auricular premature contractions	Aberrant Q R S complexes in isolated derivations and ventricular premature contractions	Delayed auriculoventricular conduction	Delayed auriculoventricular conduction and sinus arhythmia	Delayed auriculoventricular conduction, aberrant Q R S complexes in isolated derivations and ventricular premature contractions	Complete auriculoventricular dissociation	Auricular flutter	Nodal tachycardia	Ventricular tachycardia
Derivation I	140	41	0	2	0	6	0	0	11	0	0	8	6	1	0	36	3	8	4	2	2	1	2	1	0	0	3	1	1	1
Derivation III	688	550	24	14	1	8	4	1	40	0	1	17	4	0	1	10	0	2	0	0	10	0	1	0	0	0	0	0	0	0
Derivations I and II	62	32	0	2	0	2	1	0	2	1	0	3	1	0	0	11	0	1	1	1	2	0	0	1	0	0	0	0	0	1
Derivations II and III	171	112	1	5	0	1	1	0	10	1	0	20	4	0	0	4	0	5	1	1	1	0	0	1	1	0	1	0	0	1
Derivations I, II and I II	45	21	0	2	0	0	0	0	4	0	0	8	3	0	0	2	0	1	0	0	1	0	0	2	0	1	0	0	0	0
Total	1106	756	25	25	1	17	6	1	67	2	1	56	18	1	1	63	3	17	6	4	16	1	3	5	1	1	4	1	1	3

TABLE 9.—VALVULAR DISEASE ASSOCIATED WITH T WAVE NEGATIVITY

		Mitral disease						Aortic disease						
	Total	Mitral regurgitation	Mitral stenosis	Double mitral lesion	Mitral and polyvalvular regurgitation	Double mitral lesion and aortic regurgitation	Mitral stenosis and aortic regurgitation	Aortic regurgitation	Aortic stenosis	Double aortic lesion	Aortitis	Aortic regurgitation and aortitis	Aortic and polyvalvular regurgitation	Aortic and mitral regurgitation
Derivation I	37	16	0	2	1	2	0	3	2	2†	2*	5†	2†	0
Derivation III........	122	64	27	7	0	2	0	10‡	1	2	1*	2†	0	6
Derivations I and II..	14	5	0	1	1	1	1	2	1	2*	0	0	0	0
Derivations II and III.	49	22	7	5	2	0	0	4*	1	3	2*	1*	2	0
Derivations I, II and III	12	4	0	0	0	0	0	3	0	2	0	3*	0	0
Total.............	234	111	34	15	4	5	1	22	5	11	5	11	4	6

* One patient in this group had syphilitic lesions.

† Two patients in this group had syphilitic lesions.

‡ Three patients in this group had syphilitic lesions.

TABLE 10.—CARDIAC MORTALITY

T wave negativity in Derivation I

Decade	Total	Patients heard from	Males	Females	Cardiac deaths	Percentage	Living	Worse	Improved	Unchanged	No cardiac complaints
11–20	2	2	2	0	1	50.0	1	0	1	0	0
21–30	5	5	3	2	3	60.0	2	0	0	2	0
31–40	7	6	6	0	4	66.6	2	1	1	0	0
41–50	28	24	13	11	11	45.8	11	2	6	3	0
51–60	40	32	22	10	21	65.6	9	2	5	2	0
61–70	54	44	33	11	35	79.5	8	5	2	1	0
71–80	4	4	4	0	3	75.0	0	0	0	0	0
											0
Total.....	140	117	83	34	78	66.6	33	10	15	8	0

CARDIAC MORTALITY AND T WAVE NEGATIVITY

T wave negativity in Derivation I.—Information has been received concerning 117 patients having T wave negativity in Derivation I of their electrocardiograms. Seventy-eight (66.6 per cent) have died from heart disease during a period of four and one-half years (Table 10). The mortality in every decade is high; the lowest percentage (45.8) occurred between the ages of 41 and 50. Thirty-three patients are alive and 10 of these report their conditions worse, 15 are improved and eight are unchanged. None of the patients was without cardiac complaint.

The high cardiac mortality in this group is in accord with the hypothetic and clinical significance, previously emphasized, which attends this T wave negativity. To prevent misunderstanding it may be stated that the negative T wave *per se* is only the manifestation of serious underlying myocardial disorder. Changes in cardiac function affecting contraction preponderance, resulting from organic or functional myocardial fatigue, alter electropotential which produces T wave negativity.

T wave negativity in Derivation III.—Information has been received concerning 487 patients having T wave negativity in Derivation III of their electrocardiograms. Forty-six (9.4 per cent) have died from heart disease during a period of four and one-half years. The data are summarized in Table 11. This relatively low cardiac mortality is sharply contrasted with the mortality of the foregoing group. It is in agreement, however, with the hypothetical and clinical significance accorded T wave negativity in Derivation III. The potential distribution producing this negativity is but a slight departure from normal. Four hundred twenty patients are alive, 97 report their conditions worse, 161 are improved, and 162 are unchanged. One hundred six patients report no cardiac complaints.

TABLE 11.—CARDIAC MORTALITY

T wave negativity in Derivation III

Decade	Total	Patients heard from	Males	Females	Cardiac deaths	Percentage	Living	Worse	Improved	Unchanged	No cardiac complaints
1–10	10	8	3	5	2	25.0	5	0	3	2	3
11–20	62	42	9	33	2	4.7	40	7	20	13	17
21–30	190	139	22	117	5	3.5	127	30	53	44	37
31–40	161	113	27	86	9	7.9	99	23	33	43	25
41–50	138	89	24	65	9	10.1	78	18	30	30	20
51–60	83	68	37	31	13	19.1	53	13	18	22	3
61–70	39	24	15	9	5	20.8	16	6	3	7	1
71–80	5	4	3	1	1	25.0	2	0	1	1	0
Total....	688	487	140	347	46	9.4	420	97	161	162	106

TABLE 12.—CARDIAC MORTALITY

T wave negativity in combined Derivations I and II

Decade	Total	Patients heard from	Males	Females	Cardiac deaths	Percentage	Living	Worse	Improved	Unchanged	No cardiac complaints
21–30	7	5	5	0	4	80.0	1	0	0	1	0
31–40	5	3	3	0	3	100.0	0	0	0	0	0
41–50	13	11	9	2	7	63.6	3	0	2	1	1
51–60	20	19	13	6	12	63.1	7	1	5	1	0
61–70	15	12	8	4	7	58.3	5	0	5	0	0
71–80	2	2	1	1	2	100.0	0	0	0	0	0
Total....	62	52	39	13	35	67.3	16	1	12	3	1

T wave negativity in combined Derivations I and II.—Of the 52 patients having T wave negativity in combined Derivations I and II concerning whom we have heard, thirty-five (67.3 per cent) have died from heart disease during four and one half years. This mortality is greater than was anticipated in that the potential distribution resulting in this T wave negativity was not the greatest departure from normal. In Figure 115, in which the potential distribution is represented, the right upper zone becomes electropositive to the left, instead of electronegative as in the normal, but this is a lesser departure than iso-electric. The fact that the group is relatively small may be a factor in obtaining a high cardiac mortality. Sixteen patients are alive, one reports his condition worse, twelve are improved, and three are unchanged. Only one patient reports no cardiac complaint.

T wave negativity in combined Derivations II and III.—We have learned of the condition of 135 patients having T wave negativity in combined Derivations II and III. Thirty-five (25.9 per cent) have died from heart disease during a period of four and one half years (Table 13). In contradistinction to the foregoing group, the mortality was lower than expected from a hypothetic consideration of potential distribution and associated heart disease. A possible explanation for this discrepancy rests in the fact that 23.3 per cent of the patients were examined during the last year of the series, and the time element, therefore, is too short to embrace a true mortality average. Eighty-eight patients are alive, twenty-five report their conditions worse, thirty-seven are improved, and twenty-six are unchanged. Sixteen patients

TABLE 13.—CARDIAC MORTALITY

T wave negativity in combined Derivations II and III

Decade	Total	Patients heard from	Males	Females	Cardiac deaths	Percentage	Living	Worse	Improved	Unchanged	No cardiac complaints
11–20	12	9	0	9	0	0	9	2	4	3	2
21–30	45	34	11	23	9	26.4	22	7	10	5	6
31–40	39	32	9	23	5	15.6	24	7	9	8	7
41–50	34	27	16	11	8	29.6	17	4	7	6	1
51–60	28	20	15	5	6	30.0	12	2	7	3	0
61–70	12	12	9	3	6	50.0	4	3	0	1	0
71–80	1	1	1	0	1	100.0	0	0	0	0	0
Total....	171	135	61	74	35	25.9	88	25	37	26	16

TABLE 14.—CARDIAC MORTALITY

T wave negativity in combined Derivations I, II, and III

Decade	Total	Patients heard from	Males	Females	Cardiac deaths	Percentage	Living	Worse	Improved	Unchanged	No cardiac complaints
11–20	1	1	0	1	1	100.0	0	0	0	0	0
21–30	4	2	2	0	1	50.0	1	0	1	0	0
31–40	7	5	3	2	2	40.0	2	0	1	1	0
41–50	9	9	6	3	1	11.1	6	0	5	1	0
51–60	12	10	10	0	9	90.0	1	1	0	0	0
61–70	12	11	8	3	5	45.5	5	4	1	0	0
Total....	45	38	29	9	19	50.0	15	5	8	2	0

TABLE 15.—CARDIAC MORTALITY IN COMPLETE SERIES

	Total	Patients heard from	Males	Females	Cardiac deaths	Percentage	Living	Worse	Improved	Unchanged	No cardiac complaints
Derivation I.........	140	117	83	34	78	66.6	33	10	15	8	0
Derivation II.......	688	487	140	347	46	9.4	420	97	161	162	106
Derivations I and II.	62	52	39	13	35	67.3	16	1	12	3	1
Derivations II and III	171	135	61	74	35	25.9	88	25	37	26	16
Derivations I, II and III	45	38	29	9	19	50.0	15	5	8	2	0
Total.............	1106	829	352	477	213	25.6	572	138	233	201	123

report no cardiac complaints; seven of these had had thyroidectomies for hyperthyroidism and were cured.

T wave negativity in combined Derivations I, II, and III.—Patients having T wave negativity in all derivations comprised a relatively small group. Nineteen of the thirty-eight (50.0 per cent) on whom we have had reports, have died from heart disease during four and one half years (Table 14). This mortality agrees fairly well with hypothetic considerations of potential distribution and associated grave heart disease (Fig. 117). Fifteen patients are alive, five report their conditions worse, eight are improved, and two are unchanged. No patient was without cardiac complaint.

In the complete series of T wave negativity, regardless of derivation grouping, information has been received concerning 829 patients. Two hundred thirteen (25.6 per cent) have died from heart disease (Table 5).

A group of cases was compiled including those cases in which there was T wave negativity without other electrocardiographic abnormalities except ventricular preponderance. This was done with the idea of excluding disorders of cardiac action known in themselves materially to influence cardiac mortality, especially auricular fibrillation and flutter, ventricular tachycardia, delayed auriculoventricular conduction, complete auriculoventricular dissociation, and arborization block. Of the 559 patients in this group of whose condition we have learned, ninety-two (16.4 per cent) have died from heart disease (Table 6). The cardiac mortality in this group is 9.2 per cent less than that of the complete series.

TABLE 16.—CARDIAC MORTALITY

T wave negativity without other electrocardiographic abnormalities

	Total	Patients heard from	Males	Females	Cardiac deaths	Percentage	Living	Worse	Improved	Unchanged	No cardiac complaints
Derivation I..........	41	32	21	11	17	53.1	13	4	7	2	0
Derviation III	550	394	86	308	33	8.3	349	76	132	141	83
Derivations I and II..	32	29	23	6	17	58.6	12	1	8	3	1
Derivations II and III.	112	86	33	53	17	19.7	61	18	28	15	14
Derivations I, II and III	21	18	15	3	8	44.4	7	2	4	1	0
Total..............	756	559	178	381	92	16.4	442	101	179	162	98

CONCLUSIONS

1. The ventricular complexes of the electrocardiogram are the expressions of two distinct processes, impulse conduction, and muscle contraction.

2. The T wave is the expression of preponderance of contraction on one side of the line of equipotential (Eyster and Meek).

3. T wave negativity results from alteration in potential distribution from changes in contraction preponderance. Changes in contraction preponderance may result from changes in blood volume, and from organic or functional myocardial fatigue.

4. The occurrence of T wave negativity in certain isolated and combined derivations of the electrocardiogram bears a fairly definite relationship to degrees of cardiac damage.

5. The significance of T wave negativity in this series as evidence of heart disease in order of gravity is in (1) combined Derivations I and II, (2) Derivation I, (3) combined Derivations I, II, and III, (4) combined Derivations II and III, and (5) Derivation III.

6. T wave negativity in Derivation II and in combined Derivations I and III has not been observed in the Mayo Clinic, and according to the hypothesis cannot exist. Such negativity would indicate a diffuse iso-electric state of the heart which would mean cardiac standstill.

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RESULTS OF SURGICAL TREATMENT OF TWENTY-ONE CASES OF ANEURYSM*

WILLIAM O. OTT

Twenty-one cases of aneurysm, exclusive of thoracic and cirsoid aneurysms and angiomas, are reviewed and the type and location are recorded as follows:

Popliteal (1 traumatic, 1 pathologic, 2 arteriovenous)	4
Common iliac (1 traumatic-saccular, 1 pathologic? 1 traumatic diffuse)	2
External iliac (traumatic)	1
Femoral (traumatic)	1
Posterior tribial (traumatic?)	1
Obturator (1 traumatic, 1 pathologic?)	2
Common carotid (pathologic)	1
Internal carotid (arteriovenous)	1
External carotid (pathologic?)	2
Subclavian (1 arteriovenous, 2 pathologic)	3
Transverse cervical (pathologic)	1
Radial (traumatic)	1
Temporal (traumatic)	1

A complete cure was affected by operation in fourteen cases: Three of the operations were excisions with proximal and distal ligature in relatively unimportant vessels. Four were proximal ligations only, three of the external carotid artery and one of the internal iliac artery. In one case a ligature was tied about the base of the sac. In four cases a Matas reconstructive endo-aneurysmorraphy was done, in three on the popliteal artery and in one on the femoral artery. In one case a compression suture was thrown around the communication in an arteriovenous aneurysm. In one case the opening in the artery was sutured by opening the sac. Improvement in the patient's condition was obtained in two cases, by proximal ligation for a pathologic aneurysm of the common carotid in one, and by a Neff clamp placed proximally in an aneurysm of the common iliac in the other. One patient was apparently well for three years after proximal ligature of the subclavian artery for a subclavian aneurysm and then he had a sudden recurrence. One patient obtained no improvement following proximal ligation for aneuryms of the posterior tibial artery. There were three deaths in the series, one following an attempt at excision of a subclavian aneurysm after a proximal ligation two months prior had failed to relieve, one due to cerebral softening following ligature of the common carotid artery, subsequent to the application of a lead clamp, in a patient with an anteriovenous aneurysm between the internal carotid and cavernous sinus, and one from circulatory disturbance following the application of a Neff clamp proximal to an aneurysm of the common iliac artery.

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Residual disability due to circulatory disturbances in the extremity persisted in only two cases, in both following the Matas operation on the popliteal artery. In one some muscular weakness persisted for four months, in the other there was some numbness and formication in the foot, but function was good and the trouble had practically cleared up eight months after operation.

To summarize, of the twenty-one patients, fourteen were completely cured, two improved, one not improved, one had a recurrence, and three died. The most successful operations were proximal and distal ligation with excision of the sac when the aneurysm did not involve an important artery, and the Matas operation when a large trunk was involved. The results of proximal ligation were uncertain.

The results in these case, although too few to be of considerable value in drawing conclusions, seem to indicate that double ligature and excision of the sac is the method of choice in cases of aneurysm of the smaller arteries, the shutting off of whose blood supply is not followed by untoward results. The Matas operation is best suited for aneurysm of the larger vessels to the extremities, especially the lower extremities. The method of gradual occlusion with clamps gave only indifferent or poor results in the cases in which it was tried.

V

BLOOD

BLOOD TRANSFUSION*

JOHN DE J. PEMBERTON

The history of attempts to discover a means for transfusing blood is a record of alternate triumph and failure. Probably the first transfusions were performed by an Italian physician, Francesco Folli, in 1654, and by Daniel of Leipsic, in 1664. The names of Richard Lower, of England, and Jean Denys, of France, stand out as pioneers in this field. Lower began his experimental work in 1665, transfusing successfully by anastomosing the artery of one animal into the vein of another by means of a cannula or pipe.

In England, in 1818, the experiments of Blundell revived the interest of the profession. He devised an apparatus consisting of a syringe connected to a receptacle by a two-way stop cock, and to a tube which was in turn connected with a cannula for insertion into the vein of the recipient.

In 1835, Bischoff introduced the idea of injecting defibrinated blood; this method became popular for some time with a large group of workers. At a later period anticoagulants were used; these included phosphate of soda (Braxton Hicks) and minute quantities of ammonia (Richardson).

The indication for transfusion was distinctly recognized by Leisrink, in 1872. He wrote, "Transfusion is indicated in all those pathologic conditions where the blood, in quantity and quality, is so altered that it is unfit to fulfil its physiologic duties." Fryer was apparently the first American to perform the operation of transfusion.

Models of a few of the earlier instruments used for transfusion are used as illustrations in this thesis. The mechanical obstacles, however, were never so insurmountable as the tendency for rapid clotting of blood during transference from donor to recipient and the occurrence of hemolysis resulting from the employment of incompatible blood.

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Landsteiner and Shattuck independently reported the presence of isoagglutinin, and Landsteiner, in 1901, divided human beings into three groups according to the agglutinating reactions of their bloods. In 1907, Jansky proved that human beings fall into four groups and this was later confirmed by Moss, who made the important observation that hemolysis of the red blood cells never occurs without their previous agglutination.

The next important step in the development of transfusion is accredited to Professor L. Agote, of Buenos Aires. November 14, 1914, he performed the first transfusion in man by blood rendered incoagulable by the addition of a 25 per cent solution of sodium citrate for every 100 c.c. of blood. Lewisohn later determined the proper dosage of sodium citrate and popularized the method.

This is a report of a series of 1036 blood transfusions on 429 patients in the Mayo Clinic between January 1, 1915, and January 1, 1918. A summary of the results and a record of the general indications and dangers is submitted because of the belief that the most accurate test of the value of any therapeutic procedure lies in its repeated clinical application. The cases were divided into six groups according to indications for transfusion:

Group 1.—Primary (pernicious) anemia, 657 transfusions in 185 cases. The conclusions of Archibald hold good for this series of patients. He states that the greater number of patients, except those who have reached the very last stages of disease, receive immediate benefit from the transfusion of blood. Moreover, many who are in extremis and are not benefited by medical treatment alone, will show great improvement by a series of blood transfusions

Group 2.—Secondary anemia, 243 transfusions in 149 cases. The value of transfusion as a preliminary treatment is illimitable in those cases in which the resistance of the body has been impaired by chronic bleeding, malignancy, or chronic infection.

Group 3.—Bleeding, eighty-one transfusions in fifty-nine cases. The results of transfusion of blood in many patients with general oozing after operation are strikingly good; the hemorrhage usually ceases immediately and the patient's improvement is soon obvious. For postoperative bleeding in patients suffering from blood dyscrasia, transfusion is an effective hemostasis.

Group 4.—Acute toxic and septic conditions, thirty-four transfusions in twenty-five cases. The patients in this group for the most part had infections following abdominal operations. The results were not encouraging, largely because the patients were hopelessly ill before transfusion was employed. It is believed, however, that blood transfusion performed shortly after or, in some instances, before operation, offers a reasonable means of combating infection.

Group 5.—Leukemias, twenty transfusions in ten cases. As a supportive measure for the correction of the anemia transfusions in this group of patients are of value.

Group 6.—Shock, one transfusion in one case. This transfusion was without beneficial effect.

The citrate method was used in this series of cases in 1001 instances. A fresh solution of 0.24 per cent sodium citrate is employed. Following the idea of Watson a small straight intestinal needle is inserted transversely into a vein at the elbow of the previously grouped donor so as to transfix the vein to the skin. With the end of the transfixing needle the vein is steadied while a large sized Kaliski needle is passed into its lumen. The blood is received in a sterile graduated glass jar containing 30 c.c. of a 2 per cent sterile solution of sodium citrate. While the blood is running, it is well mixed with the citrate solution by means of a glass rod. After the slow steadily flowing blood has reached the 250 c.c. mark 30 c.c. more of the citrate solution are added and the blood permitted to flow until there are 500 c.c. of the mixture. The blood is either carried to the recipient's room or the recipient brought to the operating room. The needle is inserted into the recipient's vein, after the manner described, and attached by rubber tubing to a glass irrigating flask, the tubing and the bottom of the flask having been filled previously with saline solution. The citrated blood is then transferred into the flask and permitted to run slowly into the recipient's vein. Better results are to be obtained from the use of a relatively small quantity, 500 c.c. to 750 c.c., repeated in five to seven days, rather than from a single transfusion of a larger amount.

The donors are selected from young, robust persons and are grouped and tested for a Wassermann reaction previous to the time of transfusion. Whenever possible a donor in the same group as the recipient is used; otherwise a person in Group IV is taken.

In 219 transfusions (21 per cent) of this series from fifteen minutes to one hour later a slight reaction of chill and fever occurred with a temperature of 100° to 105°, with or without malaise, headache, nausea and vomiting, and diarrhea. In a small percentage of cases the transfusion was followed on the third day by an eruption of herpes. In another 15 per cent of transfusions there occurred a rise of temperature to 100° or above, not associated with chill and nausea. These were of a transitory nature, the temperature returning to normal in from twelve to thirty-six hours.

Owing to clinical errors in the blood grouping, there were twelve instances of typical group reactions in the series. Such reactions occur early after the introduction of from 50 c.c. to 100 c.c. of blood. The patient first complains of tingling pains about the precordium and later an excruciating pain localized in the lumbar region. The face slowly becomes suffused a dark red to a cyanotic hue; respirations become somewhat labored, and the pulse rate at first slow, sometimes suddenly drops as many as 20 to 30 beats a minute. The patient may lose consciousness for a few minutes. In one-half of the cases in the writer's series an urticarial eruption, generalized over the body, or limited to the face, appeared with these symptoms. Later the pulse may become very rapid and thready; the skin becomes cold and clammy, and the patient's condition is grave. In from fifteen minutes to one hour a chill occurs, followed by high fever, a temperature of 103° to 105° in which the patient may become delirious. Jaundice may appear later. The macroscopic appearance of hemoglobinuria is almost constant.

The cases in this series point out most strikingly the fact that the injection of incompatible blood, that is, blood in which the donor's cells are agglutinable by the serum of the patient, is attended by the development of symptoms of the gravest nature, and that if these are not early recognized and the transfusion concluded before the injection of a large quantity of blood, fatal results are to be expected.

THE FACTORS OF COAGULATION OF THE BLOOD IN CERTAIN PATHOLOGIC CONDITIONS*

DOROTHY FOSTER PETTIBONE

A group of forty-five cases is reported with special reference to hemorrhagic disturbances. In the group are two cases of hemophilia, seven of myelogenous leukemias, two of purpura, nine of epilepsy, twelve of jaundice (ten obstructive and two hemolytic) and thirteen of miscellaneous conditions. In each case the prothrombin, calcium salts and platelets were isolated and quantitatively estimated.

The method used for determining prothrombin time is that of Howell. Coagulation time was obtained by Lee and White's method. Calcium time was estimated according to Lee and Vincent's technic. The method employed for platelet enumeration is that described by Wright and Kinnicutt.

The coagulation time in cases of hemophilia was characteristically long. There was also a deficiency in prothrombin. Platelets were present in normal numbers and had normal retractile powers. There was apparently no deficiency in calcium. Blood of hemophiliacs may become gelatinous in a comparatively short time, but the clot is not firm and disturbance results in its breaking down. If the first clot is removed, a second imperfect clot will form which can be removed in turn. As many as six or eight clots have been removed in succession from such blood; normal blood will seldom form a second clot.

One patient with hemophilia (Case 182535) had a coagulation time of seventy-three minutes. After transfusion the coagulation time was reduced to thirty-four minutes.

One patient (Case 185593), of special note in this group, had an extremely long coagulation time although his prothrombin time was within normal limits. His mother had a normal coagulation time but a markedly delayed prothrombin time.

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There was a tendency in cases of myelocytic leukemia for prothrombin time to be prolonged beyond normal limits to form six to fourteen minutes, while coagulation time was within normal limits. It is evident that these patients have the optimum amount of calcium, as addition *in vitro* of three drops of calcium noticeably delayed coagulation.

The blood in cases of hemorrhagic purpura was deficient in platelets. There was no retraction of the clot. Estimation of platelets was of value in differentiating hemorrhagic purpuras and hemophilias.

The coagulation time in cases of epilepsy was within normal limits.

There was a marked calcium deficiency in cases of jaundice of several weeks' duration. Platelets were present in normal numbers. Coagulation time was characteristically delayed. Good effects of calcium treatment were felt after several days; cases are deemed operable when the calcium time reaches seven minutes.

Among the miscellaneous group were two cases of splenic anemia, two of splenomegaly, two of pernicious anemia, two of biliary cirrhosis, and one each of diabetes, secondary syphilis, hypernephroma, migraine, and polycythemia. As control cases they showed nothing abnormal in their factors in coagulation. Prothrombin was slightly diminished in pernicious anemia.

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VI

SKIN AND SYPHILIS

JUVENILE TABES
REVIEW OF THE LITERATURE AND SUMMARY OF SEVEN CASES*

HARRY L. PARKER

A clinical picture like the tabes dorsalis seen in adults was noted in a certain number of children with syphilitic parentage and positive findings of syphilis examined at the Mayo Clinic. This suggested the problem of investigating the literature of the past twenty years for reports and discussions of similar cases. Remak, in 1885, described the first case. Later many other cases were recorded in series by Hirtz and Lemaire, Cantonnet, Lasarew, and Marburg. Doubt no longer remained as to the existence of the juvenile type of tabes; moreover, many points were established to distinguish it from the adult type.

Juvenile tabes is more rare than juvenile paresis; there are about ten cases of the latter to one of the former in any group of juvenile neurosyphilitics. Juvenile tabes dorsalis due to inherited syphilis is much more common than that due to acquired syphilis. In all cases a close study of the serology of the patient and his immediate relatives is essential as more stress is laid on the presence of syphilis than any one other physical sign, such as ataxia.

There is no special sex difference, although tabes dorsalis is more common in the male adult, and the average age at which the diagnosis is clear is 14. A child who has developed tabes dorsalis at fourteen years of age would of necessity have inherited syphilis or would have acquired it at a very early age. The history of many cases in the literature supports the idea of early infection and there are instances of persons infected at five years of age or even earlier in life. A remarkable feature of the disease is the frequency with which the parents of the child have tabes dorsalis or paresis. This introduces the question of the specificity of spirochetes in the production of a certain type of neurosyphilis; the idea of a family predisposition to syphilitic disease of the nervous system is also suggested.

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The course of the disease is long and patients who have been followed for ten years have shown little change in that time provided they kept the clinical picture of tabes dorsalis. Frequently paresis develops and once this change is instituted the degenerative course is rapid.

It is generally agreed that while any symptoms found in the adult type of the disease may be present in the juvenile, there is a different degree of frequency of the symptoms and signs and a different order of their occurrence. Incontinence of urine and bed wetting are considered the earliest and most frequent symptoms, and next in importance are optic atrophy and blindness. Optic atrophy is more common in juvenile than in adults. Lightening pains are common and observed as often in juveniles as in adults, but are not so frequent as optic atrophy and blindness.

Sensory changes were present in many of the cases recorded, but there was some difference of opinion with regard to their frequency and severity. Ataxia was quite infrequent and was carefully noted by all observers. Two-thirds of adults with tabes have ataxia, while only one-third of juveniles with tabes are so affected. Gastric crises were present in about 19 per cent of all cases recorded and Romberg's sign was seen in about 75 per cent. Patellar reflexes were absent in about 80 per cent; this is as common a sign as in the adult type of the disease. Nonne recorded a case of juvenile tabes with Charcot joint.

Most of the literature reviewed was written before syphilis was established as the direct cause of tabes dorsalis and more stress was then laid on the presence or absence of certain physical signs in making a diagnosis. Since the most prominent sign of locomotor ataxia is ataxia, this was taken as a criterion of the presence or absence of the disease. Many cases were rejected because they were not ataxic and more were included with tabes dorsalis than should have been because they were ataxic. At present a positive history of syphilis, the Wassermann test of the blood, and the spinal fluid reaction are relied on.

Seven cases of juvenile tabes dorsalis were selected from the records of the Mayo Clinic, and studied from the point of view of symptomatology, course of the disease, and physical signs, and were compared with the cases recorded in the literature. In all seven cases Westphal's sign was present, in six some degree of diminution of sensibility was found, in four the pupils were immobile, and in three Argyll Robertson pupils were present. In three cases there was optic atrophy and in three lightening pains. In three cases there was incoördination, and in three signs of congenital syphilis, or syphilis outside the nervous system, in three hypotonia, and in two incontinence of urine. In only one was ataxia present. The serum Wassermann was triple positive in all but one case and in that case the spinal fluid test was positive. In six cases a spinal fluid examination was made; in half that number the Wassermann test was negative, but in one of these the cell count was 36. A Lange test, performed on only one patient, showed a "syphilitic curve." Points worth noting are the frequency of pupillary and sensory changes, optic atrophy, crises, lightening pains, and incoördination. Three of the spinal fluids were negative to the Wassermann test in spite of a positive blood serum. Hypotonia was present in three cases and one patient was able to adopt the most grotesque and extraordinary postures. Four patients had large irregular pupils with no reaction to light or during accommodation. This is in contrast to the more usual myosis and Argyll Robertson pupils of adults. The findings in the seven cases differ little from those of former authors, except that incontinence of urine was not so frequently found; meager physical signs, the long insidious course, and the rarity of ataxia in these seven patients agree well with what has been observed before.

SQUAMOUS-CELL EPITHELIOMA OF THE SKIN: A STUDY OF TWO HUNDRED FIFTY-SIX CASES*

ALBERT C. BRODERS

The broad term "skin cancer" usually includes basal-cell epithelioma or rodent ulcer, and squamous-cell epithelioma. As a matter of fact, the term skin cancer should include four types of epithelioma, that is, basal-cell, squamous-cell, melanotic and nonmelanotic melano-epithelioma,[4] varying in degree of malignancy with their capacity to cause death in the proportion approximately of thirty-five for the first, sixty-five for the second, and ninety-five for the last two types on the basis of 1 to 100.[3] The recognition of the type of skin cancer being dealt with is of prime importance from the standpoint of prognosis. Carcinomas which originate in the sweat and sebaceous glands should not come under this term any more than carcinoma of the breast, as they originate from the germinal cells of specialized glands of dermal origin.

POLYMORPHISM OF EPITHELIAL CELLS

No cells of the body are more prone to change their form than are epithelial cells. Not infrequently cells are seen in neoplasms, under the high power of the microscope, which bear a close resemblance to muscle cells and fibroblasts but since they can be traced directly to the basal layer of the skin, there can be no doubt with regard to their origin (Figs. 120, 121, 122, and 123).

Kettle, in his article, "Polymorphism of the malignant epithelial cell" states:

"That the malignant epithelial cell is capable of polymorphism is perfectly well recognized. The interchangeability of the acinus and the solid structure in adenocarcinoma is familiar to every one, and the origin of a squamous-cell carcinoma from columnar epithelium has

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* Thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Pathology, 1920.

This thesis is published in the Annals of Surgery, 1921, lxxiii, 141–160,

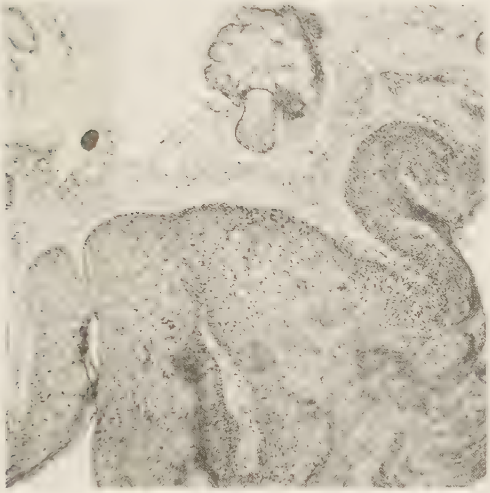

FIG. 120.—Squamous-cell epithelioma of the skin, showing polymorphism of the cells (low power).

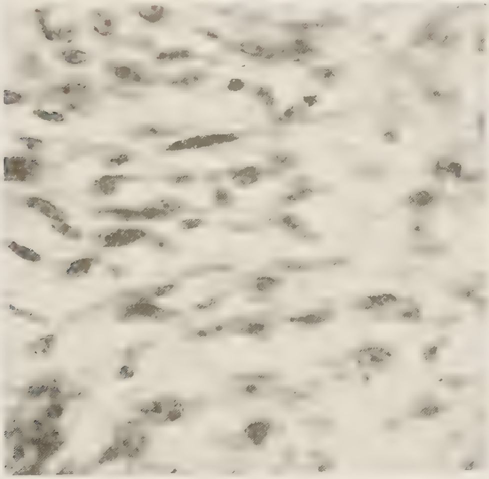

FIG. 121.—High-power magnification of section shown in Figure 120. Note the close resemblance to fibrosarcoma.

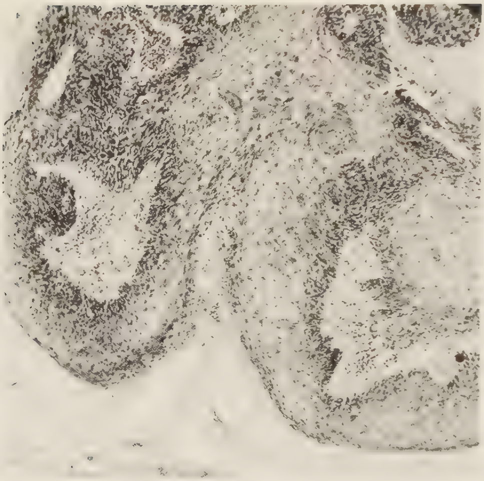

FIG. 122 (Case A33716).—Squamous-cell epithelioma of the skin showing a marked polymorphism of the cells (low power).

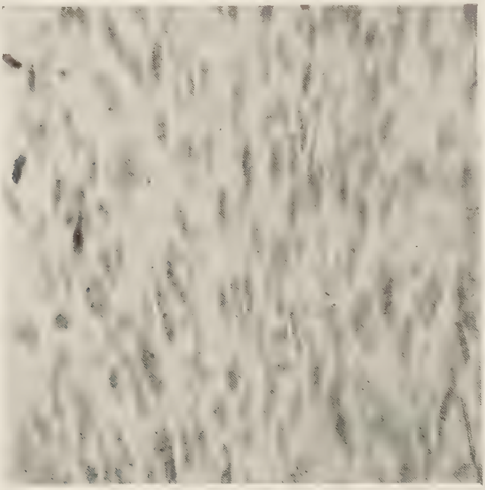

FIG. 123 (Case A33716).—High-power magnification of section shown in Figure 122. Exact picture of myosarcoma.

been reported on several occasions. Greater variations than these, however, are not, as a rule, considered possible. It is true Krompecher held that under certain conditions of growth and environment epithelial cells may assume a spindle form and may actually be converted into connective tissue elements, but his views have not found general acceptance, and the doctrine of the specific nature of cell-growth is not seriously questioned. Without going so far as to claim that the adult epithelial cell can actually become changed into a connective tissue cell, I am convinced that some carcinomata may possess such extreme powers of polymorphic growth that their cells, losing all trace of their epithelial origin, may become indistinguishable from connective tissue elements."

Krompecher's view seems somewhat illusory but considering that the entire body is developed from the fertilized ovum, his theory is brought within the range of possibility. Squamous epithelium does not originate from columnar epithelium as the columnar cell is differentiated and cannot regenerate. When a squamous-cell epithelioma develops in an organ in which columnar epithelium is found normally, the gallbladder for example, the regenerative cells which, under ordinary circumstances, produce columnar epithelium, produce squamous epithelium instead. The same process takes place in an everted uterus when protective instead of columnar epithelium is needed.

REGENERATION AND DEGENERATION

I believe that the habitual use of the term "cancerous degeneration" is incorrect. MacCarty believes that cancer is a regenerative process and not a degenerative process. Cancer tissue like other tissues degenerates. The enzyme activity of the cancer cells may cause their death and that of other cells. Cancer cells may also be destroyed by being deprived of nourishment by fibrous connective tissue. Whatever affects the general metabolism of the body affects the cancer. As is well known, the cells of our bodies are subject to the two great processes of nature, anabolic and katabolic; the former builds up and the latter tears down. Nourishing diet, fresh air, sunshine, and rest help to cure tuberculosis but not cancer which is a part of the body and when food is prepared and distributed to the normal cells it is also distributed to the cancer cells.

The chronic destruction of epithelial tissue often is followed by cancer, for example, on ulcer of the lip. The destruction of the epithelial cells is a katabolic process and the regeneration by the cells of the germinal layer is an anabolic process. If the anabolic process predominates, the ulcer is healed over by normal epithelium; if the katabolic process predominates, the ulcer continues to grow. If cancer develops on the border of the ulcer, however, the cancer has both regenerative and destructive properties. Cancer cells are undifferentiated cells which have taken over new properties beside their regenerative abilities, that is, the power to invade and migrate, thereby infringing on the rights of other cells, and, depending on their degree of cellular activity, producing death of the entire organism. I believe that pernicious anemia, myelogenous leukemia, lymphatic leukemia, and, in fact, all malignant neoplasias are regenerative-destructive processes, probably following, in the large majority of instances, excessive chronic destruction of differentiated cells, such as pernicious anemia following the chronic excessive destruction of red blood cells, and lymphatic leukemia and lymphosarcoma following the chronic excessive destruction of lymphocytes. Maud Slye, in her paper on the relation of pregnancy and reproduction to tumor growth in mice, concludes:

1. "Cancer and reproduction both being growth processes draw upon the same energy residuum and are made possible by the same food. Hence the food and energy used by one are withheld from the other.

2. "Therefore (a) if the female is constantly pregnant, energy and food are withheld from the tumor and it grows with extreme slowness. (b) If there is a hiatus between pregnancies, or a termination of pregnancy, the energy which was running into reproduction is released and diverted into tumor which grows very rapidly. (c) If tumor growth considerably antedates impregnation, the currents of energy are already being used for tumor growth and are with difficulty diverted for pregnancy, probably never wholly so.

3. "Hence, when a female is well advanced in tumor growth before impregnation there are rarely any offspring brought to birth. When offspring are delivered they are few, small, under-nourished, and rarely suckled (which in mice means there is no lactation).

4. "When tumor growth is not interfered with by pregnancy, it is (a) extremely rapid in mice which are young, well nourished, and vigorous; (b) less rapid in mice older or less vigorous or less nourished;

(c) very slow in mice which are old, feeble, under-nourished, or afflicted with a destructive complicating disease."

Miss Slye's conclusions are ample proof that cancer is a regenerative-destructive process.

CELL DIFFERENTIATION AND ACTIVITY

In a recent paper on squamous-cell epithelioma of the lip,[2] I brought out the fact that the more an epithelioma tends to differentiate, the lower is the degree of malignancy. I believe this principle can be applied to malignant neoplasia in general. Very few melanotic or nonmelanotic melano-epitheliomas show any tendency to differentiate, hence the high degree of malignancy; however, gland formations and squamous-cells are sometimes found in these neoplasms.

The question has often been asked why the basal-cell epithelioma is of such a low degree of malignancy when it is made up of undifferentiated cells. It has been suggested that basal-cell epithelioma passes through a short cycle and differentiates into basal cells, while squamous-cell epitheliomas pass through a longer cycle in order to differentiate into squamous-cells.[5]

It is well known that the most of the cells of a basal-cell epithelioma bear a close resemblance to the normal basal or regenerative cells of the epidermis; however, sometimes there are cells in this type of neoplasm which contain round nuclei with deeply staining single nucleoli, "one-eyed cells;" sometimes the nuclei are irregular in outline and contain more than one nucleolus or none. I can see no differentiation in these cells; they bear a striking resemblance to the Grade 4 squamous-cell epithelioma or the melanotic epithelioma. Whenever these cells predominate in a basal-cell epithelioma it is best to give a guarded prognosis because they are liable very rapidly to infiltrate the surrounding tissues. There seems to be no reason why a basal-cell epithelioma with such active cells should not metastasize, and maybe they do.

Frequently areas of pearly bodies are found in a basal-cell epithelioma; these are due to the change from basal cells to squamous cells and from squamous cells to pearly bodies.

The same general plan will be followed in discussing squamous-cell epithelioma of the skin as that in squamous-cell epithelioma of the lip.[2] The degree of cellular activity is graded 1 to 4 on the same basis, namely, if the epithelioma shows a marked tendency to differentiate, that is if about three-fourths of its structure is differentiated epithelium and one-fourth undifferentiated, it is graded 1 (Figs. 124, 125, and 126); if the percentage of differentiated and undifferentiated epithelium are about equal, it is graded 2 (Figs. 127, 128, and 129); if the undifferentiated epithelium forms about three-fourths and the differentiated about one-fourth of the growth, it is graded 3 (Figs. 130, 131, and 132); if there is no tendency for the cells to differentiate it is graded 4 (Figs. 133, 134, and 135). The number of mitotic figures and the number of cells with single large deeply-staining nucleoli, one-eyed cells, play an important part in the grading. With some experience in the grading of epitheliomas, a picture for each grade becomes fixed in mind, thereby making the grading rather easy. Not all cells with deeply staining nucleoli are malignant; however, when they are found in a neoplasm in large numbers it is best to treat the tumor as malignant or promalignant. These cells are regenerative, and, since malignant neoplasia is a regenerative-destructive process, their presence in malignant neoplasms is not out of order.

An endothelial leukocyte is also a one-eyed cell but it differs from the true one-eyed cell of malignant neoplasia in that it lacks body. Not all malignant cells have a single nucleolus; some have more than one and others have none. As a rule the more malignant the neoplasm, the more irregular and ill-defined are its cell nuclei; however, exceptions to this are not infrequently seen. A pearly body in a lymph node is not itself cancer; neither are the large flat squamous cells with small nuclei which lie adjacent to it. The pearly body is a finished product which corresponds to the horny layer of the epidermis. The large flat squamous cell with a small nucleus is almost a finished product; the keratinization of this cell forms the basis of the pearly body (Figs. 136 and 137). The large flat squamous cell with the small nucleus and the pearly body are not cancer when found in a lymph node as they are incapable of regeneration. Cells which are incapable of regeneration are not cancer cells. On this reasoning, the basis of grading epitheliomas is formulated.

CONCLUSIONS

1. The term "skin cancer" is indefinite and should be discarded.
2. The use of the term "cancerous degeneration" also should be discontinued.

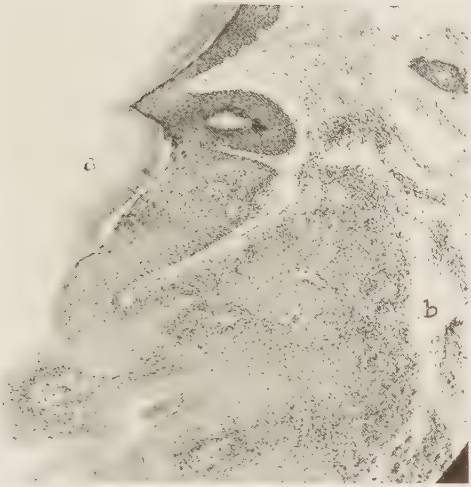

Fig. 124 (Case A19884).—Grade 1 epithelioma; *a*, normal epithelium; *b*, epithelioma showing marked differentiation.

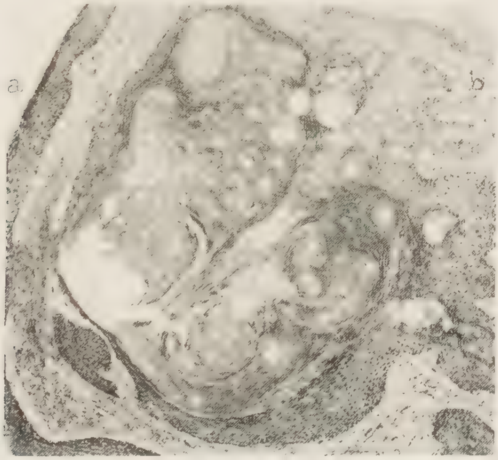

Fig. 125 (Case A60960).—Grade 1 epithelioma; *a*, normal epithelium; *b*, epithelioma showing marked differentiation.

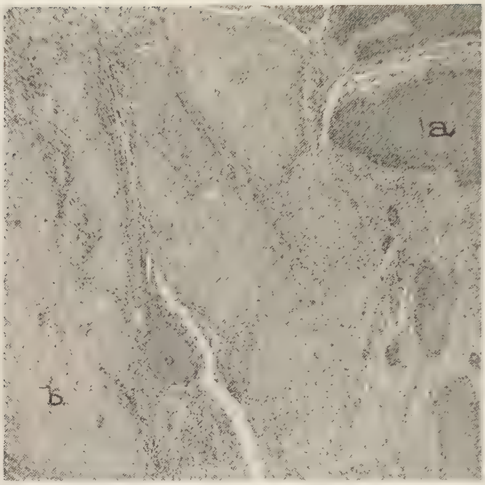

FIG. 126 (Case A95147).—Grade 1 epithelioma; *a*, normal epithelium; *b*, epithelioma showing marked differentiation.

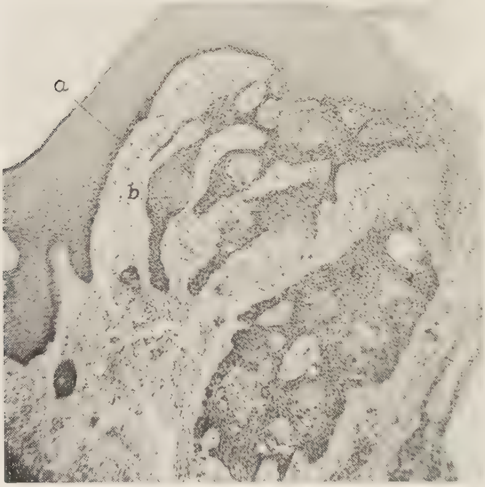

FIG. 127 (Case A75272).—Grade 2 epithelioma; *a* normal epithelium; *b*, pearly body; *c*, undifferentiated epithelial cells.

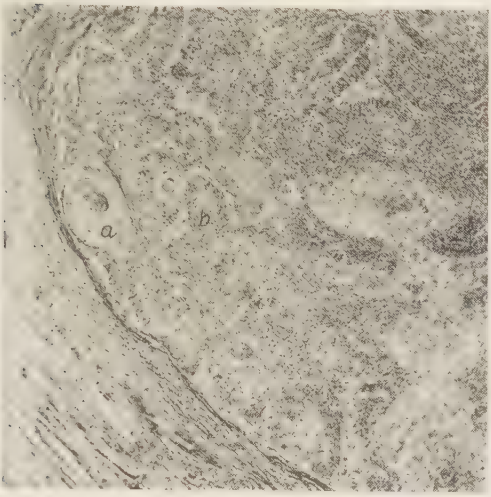

FIG. 128 (Case A90006).—Grade 2 epithelioma; *a*, pearly body; *b*, undifferentiated cells.

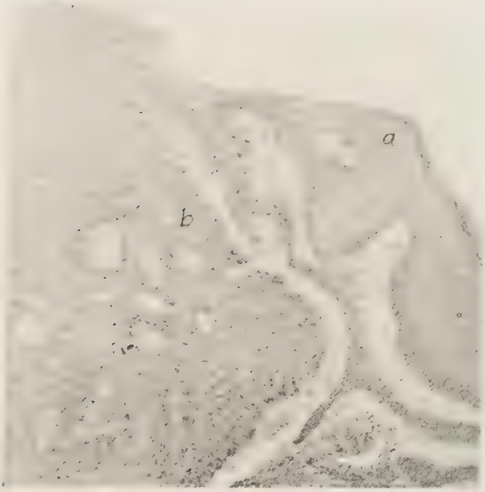

FIG. 129 (Case A34711).—Grade 2 epithelioma; *a*, normal epithelium; *b*, epithelioma.

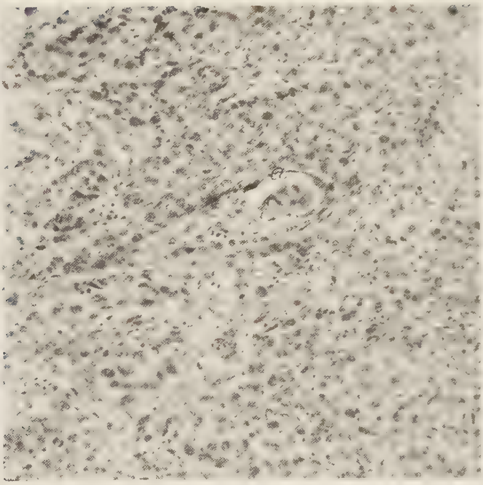

FIG. 130 (Case A53661).—Grade 3 epithelioma; *a*, epithelial cells showing practically complete differentiation.

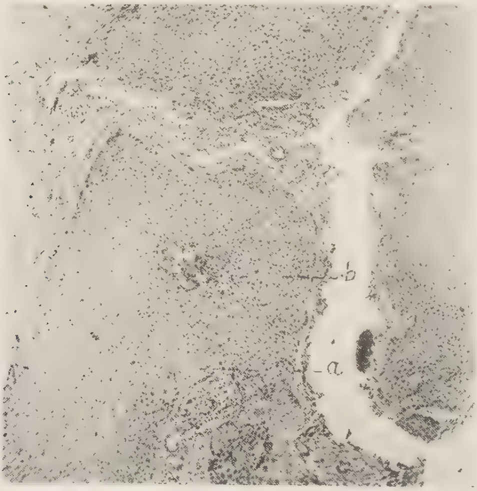

FIG. 131 (Case A220).—Grade 3 epithelioma; *a*, practically completely differentiated cells; *b*, undifferentiated cells.

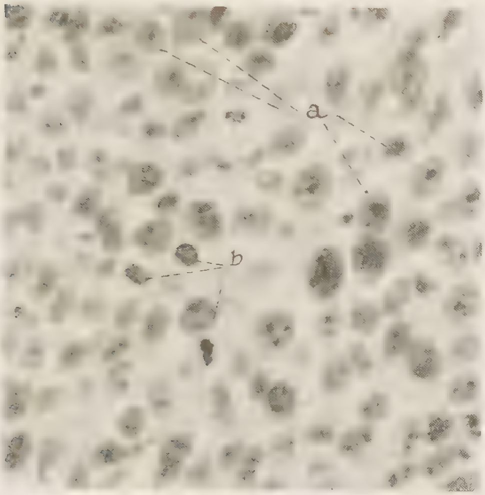

Fig. 132 (Case A38629).—Very malignant area of a Grade 3 epithelioma; *a*, "one-eyed cells"; *b*, mitotic figures. In some areas in this neoplasm the cells showed a tendency to differentiate.

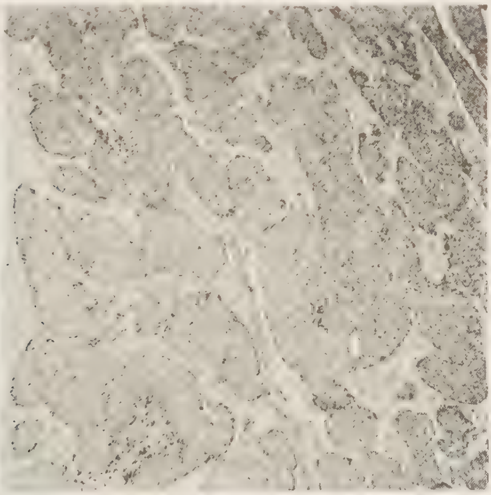

Fig. 133 (Case A90864).—Low-power magnification of a Grade 4 epithelioma, showing irregular pale-staining cells; very few one-eyed cells.

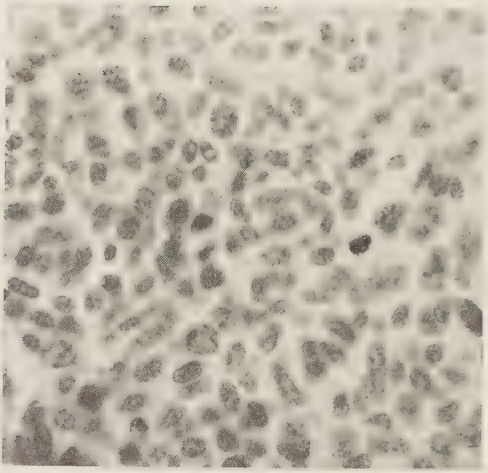

Fig. 134 (Case A90864).—High-power magnification of a Grade 4 epithelioma (Fig. 133), showing irregular pale-staining cells; very few one-eyed cells.

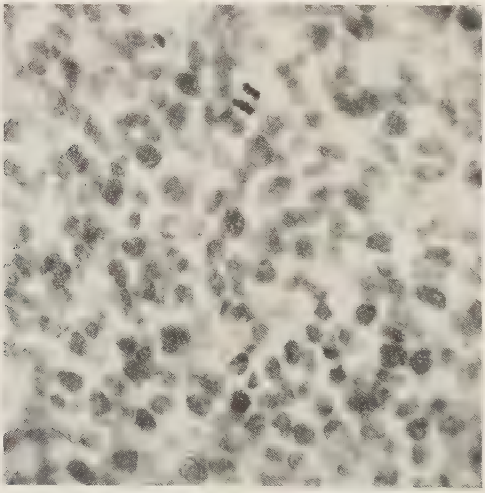

Fig. 135 (Case A118133).—High-power magnification of Grade 4 epithelioma similar to epithelioma shown in Fig. 134.

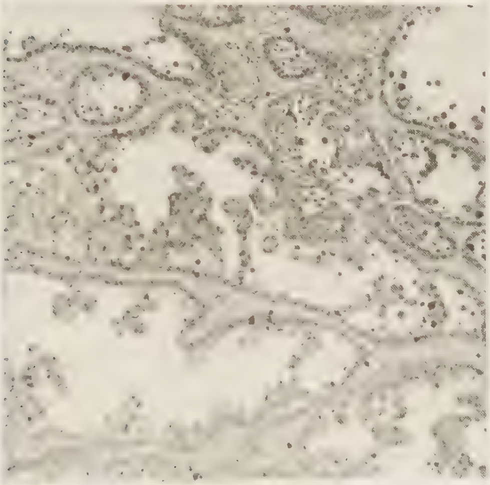

FIG. 136 (Case A56882).—Squamous-cell epithelioma of the skin, showing a number of cells undergoing keratinization (low power).

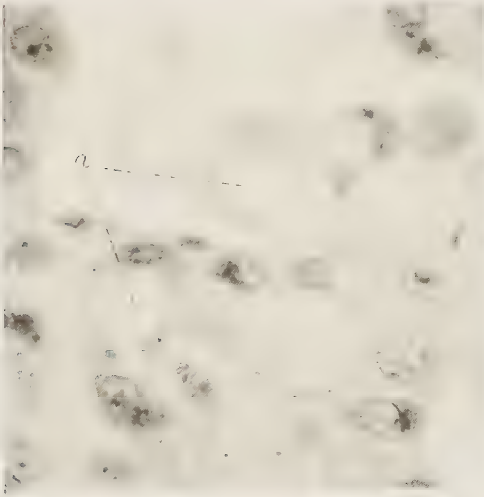

FIG 137 (Case A56882).—High-power magnification of section shown in Figure 136 *a*, cells becoming keratinized.

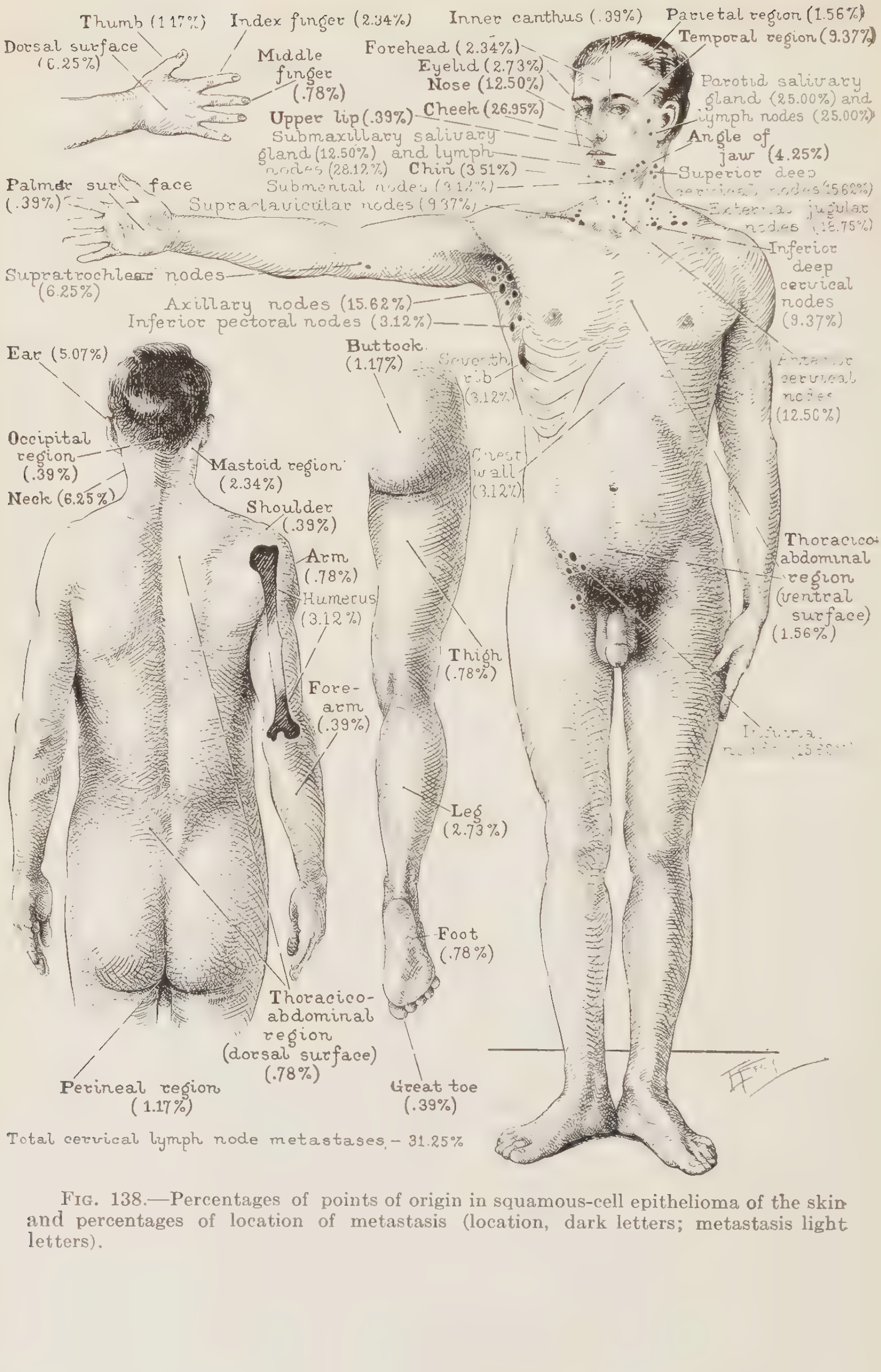

FIG. 138.—Percentages of points of origin in squamous-cell epithelioma of the skin and percentages of location of metastasis (location, dark letters; metastasis light letters).

3. The capacity of a cancer to cause death should be known when a prognosis is given.

4. Cancer is a regenerative-destructive process, resulting in the majority of instances from the interaction of anabolic and katabolic processes.

5. In most cases malignant neoplasia probably follows the chronic excessive destruction of differentiated cells.

6. As a rule, the more marked the differentiation in a squamous-cell epithelioma, the lower is the degree of malignancy.

7. Pearly bodies and large flat squamous cells with small nuclei are not cancer; cancer is regenerative or undifferentiated cells.

8. The 256 cases in this series of squamous-cell epithelioma of the skin represent 12.8 per cent of 2,000 cases of general epithelioma observed in the Mayo Clinic from November 1, 1904 to July 22, 1915.

9. Squamous-cell epithelioma of the skin occured more often in males than in females; the proportion is 4 to 1. It occured in patients past middle life; their average age was fifty-nine and thirty-four hundredths years.

10. Squamous-cell epithelioma occurred most often in farmers; they represented 53.96 per cent of the cases in males.

11. The site of the cancer was preceded by a mole, wart, pimple, scab, ulcer, leukoplakia, crack, wen, blister, or lump in 51.17 per cent of the cases.

12. There was a history of injury in 23.82 per cent of the cases; burns represented 24.59 per cent of the injuries, and x-ray burns represented 20 per cent of the burns.

13. The average duration of the lesion was 4.8 years and the average greatest diameter 3.85 cm.

14. Seventy-eight and four hundredths per cent of all the lesions occurred above the clavicle (Fig. 138).

15. Twenty-eight and twelve hundredths per cent of the patients were treated with acid, paste or plaster, and so forth, before they entered the Clinic.

16. Twenty-six and ninety-five hundredths per cent of the patients were operated on before they entered the Clinic.

17. Ninety-two and eighteen hundredths per cent of the patients were operated on at the Clinic.

18. Regional lymph nodes or salivary glands were not removed in 77.96 per cent.

19. Of the 22.03 per cent of the cases in which the regional lymph nodes or salivary glands were removed, metastasis was demonstrated in 61.53 per cent.

20. The cervical lymph nodes were involved in 31.25 per cent, submaxillary lymph nodes in 28.12 per cent, the parotid lymph nodes in 25 per cent, the parotid salivary gland in 25 per cent, and the axillary and inguinal lymph nodes each in 15.62 per cent.

21. In a classification of the epitheliomas according to cellular activity, on a basis of 1 to 4, Grade 1 represents 8.20 per cent; Grade 2, 69.53 per cent; Grade 3, 17.18 per cent, and Grade 4, 5.07 per cent.

22. The average duration of the lesion according to grade was longest in Grade 2, five and thirty-six hundredths years, and shortest in Grade 3, three and two hundredths years.

23. The average size of the lesion according to grade was largest in Grade 4, 5.4 cm. and smallest in Grade 1, 2.09 cm.

24. Fifty-one and seventy-seven hundredths per cent of the patients operated on and traced are dead and 48.22 per cent are alive.

25. Eighty-two and thirty-five hundredths per cent of the living patients report good results, having been free from the disease on an average of seven and forty-four hundredths years.

26. Information received concerning the patients operated on who died, shows that 65.51 per cent died from epithelioma.

27. Three (1.27 per cent) of the patients who were operated on died before being dismissed from the Clinic; the actual operative mortality was 0.42 per cent.

28. Patients who were treated with pastes, plasters, and so forth, before entering the Clinic did not get such good total good results as those who were not so treated, 57.14 per cent in the former group and 61.11 per cent in the latter; the total poor results were 40 per cent in the former group and 30 per cent in the latter.

29. Ten and fifty-two hundredths per cent of the patients with metastasis are living.

30. One of the two living patients who had metastasis reports a good result and one a fair result. In these patients the parotid lymph nodes and salivary gland on one side only were involved.

31. No patient with cervical lymph nodes or more than one group of any lymph nodes involved has been reported living.

32. All the patients reported dead who had metastasis died from epithelioma.

33. Sixty per cent of the patients operated on in whom no metastasis was demonstrated are living, all with good results, and 40 per cent are dead.

34. Sixty-six and sixty-six hundredths per cent of the patients reported dead who did not have metastasis died from epithelioma.

35. Fifty-three and fifteen hundredths per cent of the patients operated on in whom no regional lymph nodes or salivary glands were removed are living and 46.84 per cent are dead; 81.35 per cent of the living report good results.

36. Fifty-four and seventy-six hundredths per cent of the patients reported dead in whom no regional lymph nodes or salivary glands were removed, died from epithelioma.

37. The total good results for the patients with metastasis are 6.66 per cent; for those without metastasis, 77.77 per cent; and for those in whom no regional lymph nodes or salivary glands were removed, 66.33 per cent.

38. The total poor results without regard to grade for the patients with metastasis are 86.66 per cent; for those without metastasis, 22.22 per cent; and for those in whom no regional lymph nodes or salivary glands were removed, 25.74 per cent.

39. The average duration of the lesion in the patients with metastasis was two and sixty-seven hundredths years; in those without metastasis, five and three hundredths years; and in those in whom no regional lymph nodes or salivary glands were removed, four and seventy-eight hundredths years.

40. The average size of the lesion in the patients with metatasis was 6.3 cm.; in those without metastasis, 4.15 cm.; and in those in whom no regional lymph nodes or salivary glands were removed, 3.08 cm.

41. The known causes of deaths from epithelioma were: Grade 1, 0; Grade 2, 61.29 per cent; Grade 3, 85.71 per cent; and Grade 4, 100 per cent.

42. The total good results for Grade 1 are 92.85 per cent; Grade 2, 65.43 per cent; Grade 3, 41.66 per cent; and Grade 4, 0.

43. The total poor results for Grade 1 are 0; Grade 2, 25.92 per cent; Grade 3, 54.16 per cent; and Grade 4, 100 per cent.

TABLE 1.—SQUAMOUS-CELL EPITHELIOMA OF THE SKIN: TWO HUNDRED FIFTY-SIX CASES (12.8 PER CENT OF TWO THOUSAND CASES OF GENERAL EPITHELIOMA) FROM NOV. 1, 1904, TO JULY 22, 1915, MAYO CLINIC.

	No.	Per cent
Patients	256	
Males	205	80.078
Females	51	19.921
Age:		
Youngest patient		25.
Oldest patient		88.
Average age of patients		59.34*
Occupation (males):		
Farmer	102	53.96*
Laborer	21	11.11
Merchant	11	5.81
Railroad employee	8	4.23
Physician	6	3.17
Agent	4	2.11
Other occupations, 22 each under 2 per cent	37	19.57
Family history of malignancy	31	12.10
Previous lesion at site of cancer:		
Mole, wart, pimple, scab, ulcer, leukoplakia, crack, wen, blister, lump, etc	131	51.17
History of injury	61	23.82
Burns, proportion of total injuries	15	24.59
X-ray burns, proportion of total burns	3	20.00
Average duration of lesion		4.8 years
Longest duration of lesion		35.0 years
Shortest duration of lesion		0.057 years
Greatest diameter		30.00 cm.
Average greatest diameter		3.854 cm.

* A large proportion of patients coming to the Mayo Clinic are from rural communities.

Table 2.—Location of the Lesion (Fig. 138)

	Cases	Per cent
Single lesion	247	96.48
Multiple lesions	9	3.51
Cheek	69	26.95
Nose	32	12.50
Temporal region	24	9.37
Neck	16	6.25
Hand (dorsal surface)	16	6.25
Ear	13	5.07
Angle of jaw	11	4.25
Chin	9	3.51
Eyelid	7	2.73
Leg	7	2.73
Forehead	6	2.34
Mastoid region	6	2.34
Index finger	6	2.34
Thoracico-abdominal region (ventral surface)	4	1.56
Parietal region	4	1.56
Thumb	3	1.17
Buttock	3	1.17
Perineal region	3	1.17
Thoracico-abdominal region (dorsal surface)	2	0.78
Arm	2	0.78
Middle finger	2	0.78
Thigh	2	0.78
Foot	2	0.78
Inner canthus	1	0.39
Occipital region	1	0.39
Upper lip (near nose)	1	0.39
Shoulder	1	0.39
Forearm	1	0.39
Hand (palmer surface)	1	0.39
Great toe	1	0.39

Table 3.—Treatment Elsewhere of Squamous-cell Epithelioma of the Skin

	No.	Per cent
Nonsurgical		
One or more treatments with acids (carbolic, chromic, hydrochloric, and nitric), alum (burnt), carbon dioxid, electricity, paste, potassium iodid, radium, roentgen ray, (proportion of total non-operative methods of treatment 50 per cent) scarlet red, and silver nitrate	72	28.12
Surgical		
One or more operations	69	26.95
Surgical and nonsurgical		
Operations without treatment with acids, alum, carbon dioxid, etc.	50	19.53
Treatment with acids, alum, carbon dioxid, etc., without operation	53	20.70
Operation and treatment with acids, alum, carbon dioxid, etc.	103	40.23

TABLE 4.—PATIENTS OPERATED ON AT THE MAYO CLINIC

Patients	236 (92.18 per cent of 256)
Excision with knife immediately followed by cautery (one operation)	52 (22.03 per cent of 236)
Excision with knife (one operation)	46 (19.49 per cent of 236)
Block dissection of neck (unilateral) either alone or combined with other operations or methods of treatment before, at the same time, or after the block dissection was performed	9 (3.81 per cent of 236)
Cautery (one operation)	8 (3.38 per cent of 236)
Excision with cautery (one operation)	7 (2.96 per cent of 236)
Excision with knife immediately followed by cautery (one operation) and later by skin graft (one operation)	7 (2.96 per cent of 236)
Amputation of one or more fingers or of thumb and removal of regional lymph nodes at the time of amputation or after amputation and either associated with or not associated with other operative or nonoperative treatment before, at the time of, or after amputation	6 (2.54 per cent of 236)
Amputation of thigh or leg with or without removal of regional lymph nodes and either associated or not associated with other operative or nonoperative treatment before, at the time of, or after amputation	5 (2.11 per cent of 236)
Amputation of arm, forearm, or hand with removal of regional lymph nodes before or at the time of amputation, and either associated or not associated with other operative or nonoperative treatment before, at the time of, or after the amputation	5 (2.11 per cent of 236)
Excision with knife immediately followed by cautery (one operation) and followed later by cautery (one operation)	4 (1.69 per cent of 236)
Cautery (two operations)	4 (1.69 per cent of 236)
Block dissection of neck (bilateral) (two operations) accompanied by a complete evisceration of the left eye, excision of eyelids, and one supraclavicular lymph node preceded by three excisions with knife immediately followed by cautery	1 (0.423 per cent of 236)
Miscellaneous (various combinations of operations, radium, and roentgen rays)	82 (34.74 per cent of 236)
Inoperable	16 (6.25 per cent of 236)
Operation refused after diagnosis had been made	4 (1.56 per cent of 236)
Cases in which no lymph nodes or salivary glands were removed	184 (77.96 per cent of 236)
Cases in which lymph nodes or salivary glands were removed (one or more groups)	52 (22.03 per cent of 236)

Table 5.—Lymph Nodes and Salivary Glands Removed in Fifty-two Cases

	Cases	Per cent
Submaxillary lymph nodes	23	44.23
Submaxillary salivary glands	23	44.23
External jugular nodes	20	38.46
Superior deep cervical nodes	15	28.84
Anterior cervical nodes	12	23.07
Inferior deep cervical nodes	12	23.07
Cervical lymph nodes removed	21	40.38
Parotid salivary gland	10	19.21
Parotid lymph nodes	9	17.30
Submental nodes	9	17.30
Axillary nodes	9	17.30
Inguinal nodes	6	11.53
Supratrochlear nodes	3	5.76
Supraclavicular lymph nodes	3	5.76
Chest wall	1	1.92

Table 6.—Pathologic Findings in Fifty-two Cases in Which Lymph Nodes and Salivary Glands were Removed

	Cases	Per cent
No metastasis	20	38.46
Metastasis	32	61.53
Inguinal lymph nodes alone (one side)	5	15.62
Axillary lymph nodes alone (one side)	3	9.37
Parotid salivary gland and lymph nodes (one side)	5	15.62
Submaxillary lymph nodes alone (one side)	2	6.25
Submaxillary salivary gland and lymph nodes (one side)	2	6.25
Right and left external jugular, submental, left submaxillary and supraclavicular lymph nodes	1	3.12
External jugular, anterior cervical, superior and inferior deep cervical lymph nodes (one side)	1	3.12
Supratrochlear and axillary lymph nodes, lower and upper end of humerus, chest wall including seventh rib, axillary line (one side)	1	3.12
Miscellaneous (submaxillary lymph nodes and salivary glands, parotid lymph nodes and salivary glands, cervical, supraclavicular, supratrochlear, axillary, and inferior pectoral lymph nodes, alone or in various combinations (one side)	12	37.50

TABLE 7.—METASTASIS IN THIRTY-TWO CASES (FIG. 138)

	Cases	Per cent
Submaxillary lymph nodes	9	28.12
Parotid lymph nodes	8	25.00
Parotid salivary gland	8	25.00
External jugular lymph nodes	6	18.75
Superior deep cervical lymph nodes	5	15.62
Axillary lymph nodes	5	15.62
Inguinal lymph nodes	5	15.62
Submaxillary salivary gland	4	12.50
Anterior cervical lymph nodes	4	12.50
Inferior deep cervical lymph nodes	3	9.37
Supraclavicular lymph nodes	3	9.37
Supratrochlear lymph nodes	2	6.25
Submental lymph nodes	1	3.12
Inferior pectoral lymph nodes	1	3.12
Chest wall	1	3.12
Lower and upper ends of humerus	1	3.12
Seventh rib, axillary line	1	3.12
Cervical lymph node involvement	10	31.25

TABLE 8.—GRADES ON A BASIS OF 1 TO 4 ACCORDING TO CELLULAR ACTIVITY IN 256 CASES

	Cases	Per cent
Grade 1	21	8.20
Grade 2	178	69.53
Grade 3	44	17.18
Grade 4	13	5.07

DURATION AND SIZE OF EPITHELIOMA

	Grade 1, years	Grade 2, years	Grade 3, years	Grade 4, years
Longest duration	20.00	35.00	10.00	20.00
Shortest duration	0.08	0.05	0.16	0.10
Average duration	4.76	5.36	3.02	3.30
	Cm.	Cm.	Cm.	Cm.
Largest size	4.30	30.00	14.00	15.00
Smallest size	0.50	0.30	1.20	0.60
Average size	2.09	3.70	4.61	5.40
	Grade 1	Grade 2	Grade 3	Grade 4
Operable epithelioma	21	164	39	12
Inoperable epithelioma	0	11	4	1

OPERATION REFUSED AFTER DIAGNOSIS HAD BEEN MADE

Grade 1	Grade 2	Grade 3	Grade 4
0	3	1	0

TABLE 9.—GENERAL ULTIMATE RESULTS

Patients traced (operable, 141; inoperable, 5; refused operation, 1)	147 (57.42 per cent of 256)
Patients operated on	141
Patients living	68 (48.22 per cent)
Good result	56 (82.35 per cent of 68)
Fair result	9 (13.23 per cent of 68)
Poor result	3 (4.41 per cent of 68)

DURATION OF LIFE SINCE LAST OR ONLY OPERATION

	Good result, years	Fair result, years	Poor result, years
Longest	13.16	12.05	5.23
Shortest	4.31	5.50	0.15
Average	7.44	8.78	3.28
Patients dead	73 (51.77 per cent)		

DEATHS

Patients	79 (53.74 per cent of 147)
Patients with operable epithelioma	73 (92.40 per cent of 79)
Patients with inoperable epithelioma	5 (6.32 per cent of 79)
Patients who refused operation after diagnosis had been made	1 (1.26 per cent of 79)

CAUSE OF DEATH OF PATIENTS OPERATED ON: DATA FROM RELATIVE, HOME PHYSICIAN, OR PATHOLOGIC RECORDS OF THE CLINIC

	No.	Per cent
Known cause	58	
Epithelioma	38	65.51
Old age	4	6.89
Heart disease	4	6.89
Paralysis	3	5.17
Pneumonia	2	3.44
Arteriosclerosis	1	1.72
Acute gastritis	1	1.72
Carcinoma of pancreas	1	1.72
General infection	1	1.27
Carcinoma of prostate and pneumonia	1	1.72
Influenza	1	1.72
Tuberculosis	1	1.72
Unknown	15	

CAUSE OF DEATH OF PATIENTS OPERATED ON WHO DIED AT THE CLINIC

Epithelioma and pneumonia (1.28 years after operation)	1
Carcinoma of prostate and pneumonia (0.47 years after operation)	1
Epithelioma and shock (0.027 year after operation)	1
Total	3 (1.27 per cent of 236))
Actual operative mortality	1 (0.42 per cent of 23 6

Table 10.—Patients Operated on Treated with Pastes, Plasters, Acids, and so forth Before Entering the Clinic

	Grade 1	Grade 2	Grade 3	Grade 4	
Information received					36(54.54 per cent of 66)
Patients living					21(58.33 per cent of 36)
Good results	2(10.52 per cent of 19)	14(73.68 per cent of 19)	3(15.78 per cent of 19)		
Fair result		1(100 per cent of 1)			
Poor result			1(100 per cent of 1)		
Patients dead					15(41.66 per cent of 13)
Good result		1(100 per cent. of 1)			
Poor result		9(69.23 per cent of 13)	3(23.07 per cent of 13)	1(7.69 per cent of 13)	
Cause unknown		1			

Total Results

Good (patients recovered from epithelioma and are living or recovered from epithelioma and died from other cause)	20(57.14 per cent of 35)
Fair (patient living with slight recurrence)	1(2.85 per cent of 35)
Poor (patients living with no improvement or died from epithelioma)	14(40.00 per cent of 35)
No information received	30(45.45 per cent of 66)

Table 11.—Patients Operated on not Treated with Pastes, Plasters, Acids, and so forth Before Entering the Clinic

	Grade 1	Grade 2	Grade 3		
Information received					104(61.17 per cent of 170)
Patients living					46(44.23 per cent of 104)
Good result	4(11.11 per cent of 36)	27(75 per cent of 36)	5(13.88 per cent of 36)		
Fair result	2(25.00 per cent of 8)	5(62.50 per cent of 8)	1(12.50 per cent of 8)		
Poor result		2(100 per cent of 2)			
Patients dead					58(55.76 per cent of 104)
Good result	6(31.57 per cent of 19)	11(57.89 per cent of 19)	2(10.52 per cent of 19)		
Poor result		11(44.00 per cent of 25)	8(32.00 per cent of 25)	6 (24.00 per cent of 25)	
Cause unknown	2	10	2		

Total Results

Patients living	2(10.52 per cent of 19)
Good (patients recovered from epithelioma and are living, or recovered from epithelioma and died from other causes)	55(61.11 per cent of 90)
Fair (patients living with slight recurrence	8(8.88 per cent of 90)
Poor (patients living with no improvement or died from epithelioma	27(30.00 per cent of 90)
No information received	66(38.82 per cent of 170)

TABLE 12.—PATIENTS WITH METASTASIS OPERATED ON WITH REMOVAL OF REGIONAL LYMPH NODES OR SALIVARY GLANDS

	Grade 21	Grade 3	Grade 4	
Information received				19(59.37 per cent of 32)
Patients living			Grade 4	2(10.52 per cent of 19)
Good result*	1(100 per cent of 1)			
Fair result*		1(100 per cent of 1)		
Patients dead				17(89.47 per cent of 19)
Poor result	4(30.76 per cent of 13)	4(30.76 per cent of 13)	5(38.46 per cent of 13)	
Cause unknown	2	2		

TOTAL RESULTS

Good (patient recovered from epithelioma)	1(6.66 per cent of 15)
Fair (patient living with slight recurrence)	1(6.66 per cent of 15)
Poor (patients died from epithelioma)	13(86.66 per cent of 15)

CAUSE OF DEATH

Epithelioma	13(100 per cent of 13)
No information received	13(40.62 per cent of 32)

* In the patient who reported a good result and in the one who reported a fair result, the parotid lymph nodes and salivary glands on only one side were involved.

TABLE 13.—PATIENTS WITHOUT METASTASIS OPERATED ON WITH REMOVAL OF REGIONAL LYMPH NODES OR SALIVARY GLANDS

	Grade 1	Grade 2	Grade 3	
Information received				10(50.00 per cent of 20)
Patients living				6(60.00 per cent of 10)
Good result	2(33.33 per cent of 6)	3(50.00 per cent of 6)	1(16.65 per cent of 6)	
Patients dead				4(40.00 per cent of 10)
Good result		1(100 per cent of 1)		
Poor result		2(100 per cent of 2)		
Cause unknown		1		

TOTAL RESULTS

Good (patients recovered from epithelioma and are living or recovered from epithelioma and died from other causes)	7(77.77 per cent of 9)
Poor (patients died from epithelioma)	2(22.22 per cent of 9)

CAUSE OF DEATH

Epithelioma	2(66.66 per cent of 3)
Heart disease	1(33.33 per cent of 3)
No information received	10(50.00 per cent of 20)

TABLE 14.—PATIENTS OPERATED ON WITHOUT REMOVAL OF REGIONAL LYMPH NODES OR SALIVARY GLANDS

	Grade 1	Grade 2	Grade 3	Grade 4	
Information received					111(60.00 per cent of 185
Patients living					59(53.15 per cent of 111)
Good result	5(10.41 per cent of 48)	35(75.00 per cent of 43)	7(14.58 per cent of 48)		
Fair result	1(12.50 per cent of 8)	7(87.50 per cent of 8)			
Poor result		2(66.66 per cent of 3)	1(33.33 per cent of 3)		
Patients dead					52(46.84 per cent of 111)
Good result	7(36.84 per cent of 19)	10(52.63 per cent of 19)	2(10.52 per cent of 19)		
Poor result		14(60.86 per cent of 23)	7(30.43 per cent of 23)	2(8.69 per cent of 23)	
Cause unknown	2	8			

TOTAL RESULTS

Good (patients recovered from epithelioma and are living or recovered from epithelioma and died from other cause)	67(66.33 per cent of 101)
Fair (patients living with slight recurrence)	8(7.92 per cent of 101)
Poor (patients living with no improvement or died from epithelioma)	26(25.74 per cent of 101)

CAUSE OF DEATH

Epithelioma	23(54.76 per cent of 42)
Old age	4(9.52 per cent of 42)
Paralysis	3(7.14 per cent of 42)
Heart disease	3(7.14 per cent of 42)
Pneumonia	2(4.76 per cent of 42)
Acute gastritis	1(2.38 per cent of 42)
Arteriosclerosis	1(2.38 per cent of 42)
Carcinoma of pancreas	1(2.38 per cent of 42)
Carcinoma of prostate and pneumonia	1(2.38 per cent of 42)
General infection	1(2.38 per cent of 42)
Influenza	1(2.38 per cent of 42)
Tuberculosis	1(2.38 per cent of 42)
No information received	74(40.00 per cent of 185)

TABLE 15.—PATIENTS WITH METASTASIS AND PATIENTS WITHOUT METASTASIS OPERATED ON AND PATIENTS IN WHOM NO REGIONAL LYMPH NODES OR SALIVARY GLANDS WERE REMOVED

	Grade 1	Grade 2	Grade 3	Grade 4
With metastasis		11(34.2 per cent of 32)	12(37.5 per cent of 32)	9(28.12 per cent of 32)
Without metastasis	2(10 per cent of 20)	14(70.00 per cent of 20)	4(20.00 per cent of 20)	
Without removal of regional lymph nodes or salivary glands	19(10.32 per cent of 184)	139(75.64 per cent of 184)	23(12.5 per cent of 184)	3(1.63 per cent of 184)

DURATION OF LESION BEFORE PATIENTS' EXAMINATIONS AT THE CLINIC

With metastasis		Longest, 15 years	Shortest, 0.10 years	Average, 2.67 years
Without metastasis		Longest, 20 years	Shortest, 0.8 years	Average, 5.3 years
Without removal of regional lymph nodes or salivary glands		Longest, 35 years	Shortest, 0.05 years	Average, 1.78 years

SIZE OF LESION AT THE TIME OF PATIENTS' EXAMINATION AT THE CLINIC

With metastasis		Largest, 30 cm.	Smallest, 1.5 cm.	Average, 6.3 cm.
Without metastasis		Largest, 15 cm.	Smallest, 1.5 cm.	Average, 4.15 cm.
Without removal of regional lymph nodes or salivary glands		Largest, 30 cm.	Smallest, 0.3 cm.	Average, 3.08 cm.

Table 16.—Duration of Life after Operation of Patients with Metastasis

Information received.............................. 14(43.75 per cent of 32)

	Grade 1	Grade 2	Grade 3	Grade 4	
Patients living					2
					Years
Good result	....	1	....	.....	4.8
Fair result	....	1	....	.....	11.8
Patients dead					12
Poor result	....	4	3	5	
		Years	Years	Years	Average of all grades, years
Longest	....	1.28	0.50	2.96	2.96
Shortest	....	0.15	0.31	0.027	0.027
Average	....	0.68	0.41	1.58	0.98

No information received.............................. 18(46.25 per cent of 32)

Table 17.—Duration of Life after Operation of Twenty Patients without Metastasis

Information received.............................. 8(40.00 per cent of 20)

	Grade 1	Grade 2	Grade 3	Grade 4	
Patients living					6
Good result	2	3	1	....	
	Years	Years	Years		Average of all grades, years
Longest	7.26	7.97	8.90	....	8.90
Shortest	6.01	6.33	....	....	6.01
Average	6.63	7.18	....	....	7.29
Patients dead					2
Good result	....	1	....		
Poor result	....	1	....		
Longest	....	1.33	. . .	....	1.33
Shortest	....	0.37	....	...	0.37
Average	....	0.85	.	..	0.85

No information received.............................. 12(60.00 per cent of 20)

TABLE 18.—DURATION OF LIFE OF PATIENTS OPERATED ON WITHOUT REMOVAL OF REGIONAL LYMPH NODES OR SALIVARY GLANDS

	Grade 1	Grade 2	Grade 3	Grade 4	
Patients living					49
Good result	5	37	7	....	
	Years	Years	Years		
Longest	6.49	13.14	10.88	....	
Shortest	4.93	4.31	6.04	....	
Average	5.70	7.74	7.59	....	
Fair result	1	7			
Longest	1.59	12.50	....	....	
Shortest	....	5.50	...	....	
Average	....	8.38	....	...	
Poor result	....	2	1		
Longest	....	5.23	0.15		
Shortest	....	4.46	....	...	
Average	....	4.84	....	...	

DURATION OF LIFE OF PATIENTS OF ALL GRADES

	Good result, years	Fair result, years	Poor result, years
Patients living			
Longest	13.14	12.50	5.23
Shortest	4.31	1.59	0.15
Average	7.51	8.40	3.73
Patients dead (not from epithelioma)	6	10	2
Good result			
Longest	8.16	9.02	6.40
Shortest	0.43	0.26	5.34
Average	3.96	3.55	5.87
Poor result	13	7	2
Longest	3.61	1.95	0.98
Shortest	0.26	0.05	0.58
Average	1.45	0.93	0.78

DURATION OF LIFE AFTER OPERATION OF PATIENTS OF ALL GRADES

	Good result, years	Poor result, years	Average of all grades, years
Longest	9.02	3.61	9.02
Shortest	0.26	0.05	0.05
Average	3.92	1.22	2.45

TABLE 19.—RESULTS FOLLOWING OPERATION

	Grade 1	Grade 2	Grade 3	Grade 4
Information received	16(76.19 per cent of 21)	92(56.09 per cent of 164)	26(66.66 per cent of 39)	7(58.33 per cent of 12)
Patients living	8(50.00 per cent of 16)	50(54.34 per cent of 92)	10(38.46 per cent of 26)	
Good result	7(87.50 per cent of 8)	41(82.00 per cent of 50)	8(80.00 per cent of 10)	
Fair result	1(12.50 per cent of 8)	7(14.00 per cent of 50)	1(10.00 per cent of 10)	
Poor result		2(4.00 per cent of 50)	1(10.00 per cent of 10)	
Patients dead	8(50.00 per cent of 16)	42(45.65 per cent of 92)	16(61.53 per cent of 26)	7(100 per cent of 7)
Good result	6(100 per cent of 6)	12(38.70 per cent of 31)	2(14.28 per cent of 14)	
Poor result		19(61.29 per cent of 31)	12(85.71 per cent of 14)	7(100 per cent of 7)
Not stated	2	11	2	
Total good result (patients recovered from epithelioma and are living or recovered from epithelioma and died from other cause)	13(92.85 per cent of 15)	53(65.43 per cent of 81)	10(41.66 per cent of 24)	
Total fair result (patients living with slight recurrence	1(7.14 per cent of 14)	7(8.64 per cent of 81)	1(4.16 per cent of 24)	
Total poor result (patients living with no improvement or died from epithelioma		21(25.92 per cent of 81)	13(54.16 per cent of 24)	7(100 per cent of 7)
Total result not stated	2	11	2	

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VII

NERVOUS SYSTEM

STUDIES ON THE SPINAL CORD AND MEDULLA OF CYCLOSTOMES WITH SPECIAL REFERENCE TO THE FORMATION AND EXPANSION OF THE ROOF PLATE AND THE FLATTENING OF THE SPINAL CORD*

WILLIAM F. ALLEN

From a study of the formation of the fourth ventricle in several vertebrates, a study of a somewhat similar structure in the spinal cord of Polistotrema, and a study of the development of the spinal cord in Cyclostomes, by means of transverse sections, immediately before and during the time that the greatest depression of the spinal cord was taking place in Polistotrema and Petromyzon, the following conclusions were drawn:

In the development of the roof plate expansion (tela chorioidea) in the medulla oblongata of most vertebrates three separate stages of expansion are recognized.

1. A first enlargement of the dorsal part of the central canal takes place from a migration outward and upward of certain of the roof plate cells.

2. A second stage in the expansion of the roof plate is the direct result of an increase in pressure from the cerebrospinal fluid produced from at least two possible sources, first, in the lower vertebrates, as a consequence of considerable embryonic cerebrospinal fluid being forced into the fourth ventricle from the closure of the dorsal and ventral portions of the embryonic central canal in the spinal cord, and the ventral portion of the embryonic central canal in the medulla through the union and fusion of corresponding portions of the lateral plates, and, second, in all vertebrates through the production of cerebrospinal fluid by the walls of the fourth ventricle assuming the

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function of infiltration, diffusion, and secretion. That the ventral portion of the medulla was not expanded in the same way was explained by the fact that it was reinforced at a very early stage by nerve fibers and supported by a growing notochord.

3. A third and final stage in the expansion of the roof plate in the higher vertebrates is brought about by the appearance of a pontine flexure acting on a thin-roofed medulla filled with cerebrospinal fluid, itself under moderate pressure.

The main factor involved in the flattening of the spinal cord in Cyclostomes is the pronounced growth of the notochord; the plastic embryonic spinal cord is surrounded by structures decidedly favorable for bringing about a depression of the spinal cord through this agency. That a similar depression did not take place in the higher vertebrates is explained by the fact that the notochord is relatively a transitory and insignificant structure, while in the Cyclostomes it is not only formed early in embryonic life, but grows rapidly and continuously.

THE GROWTH OF THE BRAIN AND OF THE SPINAL CORD IN THE HUMAN FETUS*

HALBERT L. DUNN

This study was made with the purpose of securing a knowledge of the growth of the human central nervous system and of its component parts in prenatal life. Observations were made on the brains and their parts and on the spinal cords of 156 fetuses ranging from 4 cm. to 54 cm. in crown-heel length. The data thus secured were analyzed by graphic and statistical methods and the results, so far as practicable, reduced to simple empirical formulas.

The results summarized are as follows:

1. The curve of the absolute volume of the central nervous system shows a relatively slow growth but a steady increase from the second to the fourth fetal month and a more rapid growth from the fourth month to birth.

2. The rate of growth of the entire brain decreases rapidly to the seventh fetal months and then more gradually until birth.

3. The curve of the absolute volume of the cerebral hemispheres increases more rapidly in the last five fetal months.

4. The rate of growth of the cerebral hemispheres steadily decreases to birth.

5. The absolute growth of the cerebral hemispheres in the anterio-posterior axis is accompanied by a constant diminution in the rate of growth of this axis.

6. The absolute growth of the cerebral hemispheres in the transverse axis is accompanied by a steady decrease in the rate of growth.

7. The curve of the absolute volume of the cerebellum shows a slow, constant growth from the fourth to the middle of the sixth fetal month and a remarkable increase (ten-fold) thereafter.

8. The rate of growth of the cerebellum is low in the early part of fetal life, rises to a maximum at the sixth month, and then declines.

9. The percentage of the cerebellum is about 3.5 of the entire brain volume up to the sixth fetal month, and increases to approximately 6 per cent at birth.

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* Abstract of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Arts, 1920.

10. The absolute length and height of the vermis cerebelli increases steadily and at a constant absolute rate during fetal life.

11. The rate of growth of the vermis cerebelli (height and length) after the middle of the third fetal month is greater than any other percentage increment curve based on a straight line measurement.

12. The curve of the absolute volume of the pons and medulla rises rapidly to the sixth fetal month and still more rapidly thereafter.

13. The volume of the pons and medulla decreases from 5.5 per cent of the entire brain volume in the fourth fetal month to 1.4 per cent at birth.

14. The curve of the absolute length of the pons increases rapidly to the sixth fetal month and steadily but less rapidly from this time to birth.

15. The curve of the absolute mid-brain volume shows a gradual increase during prenatal life; while the rate of growth portrays a steady decrease.

16. The entire midbrain exhibits the growth of a true brain part while the colliculi represent merely a demarcation of the brain-stem.

17. The curve of the absolute volume of the spinal cord increases regularly from the fifth fetal month until birth.

18. The rate of growth of the spinal cord (volume) decreases from the fourth fetal month to birth.

19. The curve of the absolute length of the spinal cord shows a rapid increase prior to the fifth fetal month, after which time the increase is slower.

20. The rate of growth in the length of the spinal cord is relatively high in the third and fourth fetal months; after this time it falls gradually to birth.

21. The growth of the brain and spinal cord includes four distinct types: (a) cerebral growth which shows a steady constant growth throughout fetal life; (b) brain stem and cord growth, which increases much faster previous to the fifth fetal month than it does in the last four fetal months; (c) cerebellum growth, which lags until the sixth fetal month, from which time until birth it exceeds in growth activity the other parts of the central nervous system; and (d) compound growth, illustrated in the growth of the entire central nervous system, which represents the combined effect, predominated by the growth of the cerebrum, the largest part.

THE PATHOGENESIS OF THE LESIONS OF THE NERVOUS SYSTEM IN CASES OF PERNICIOUS ANEMIA*

CHARLES E. NIXON

HISTORICAL REVIEW

Since Lichtenstern and Lichtheim noted changes in the spinal cord in cases of pernicious anemia many observers have offered their explanation of the mechanism by which these lesions are produced.

That the blood picture of this disease is produced by a toxin there is fairly general agreement. In summarizing the theories regarding the genesis of pernicious anemia Squire mentions:

1. Splenic disturbances.
2. A general disturbance of the lipoid mechanisms and functions of the body, thus the liberation of hemolytically active substances, as oleic acid.
3. Gastro-intestinal disturbances leading to the destruction of sufficient mucosa to allow undigested proteins to leak through into the blood stream where their digestion (parenteral) liberates protein poison.

While the majority of neuropathologists believe that the lesions of the nervous system are caused by a toxin they are not agreed as to the way the toxin acts. Seyderhelm has recently made an interesting contribution to this phase of the subject. He was able to break up the toxin "Oestrin" into various fractions. The toxin was both hemolytic and neurotoxic; he found that the "blood poison" acts ("both as a hemolytic and toxic agent") only by parenternal introduction.

It is not without historical interest to note the suggestion which has been made that anemia may sometimes be of central origin. Herrick gives a number of case reports in which pernicious anemia or severe anemia followed nervous shock. Pokrowski found changes in the cerebellum, fourth ventricle and medulla, and was led to conclude

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"that the findings in the central nervous system must have had an influence, if not the sole influence in the production of the anemia." Schuele and others have also referred to the possibility of the anemia being of neurogenic origin.

The various theories that have been advanced to explain the lesions found in the cord and brain in pernicious anemia may be summarized as follows:

1. Hemorrhagic foci:—It is supposed that numerous small extravasations of blood occur causing secondary degeneration.

2. Primary vascular changes:—These consist in thickening of the vessel wall, exudation around the vessel or thrombosis. Through coalesence of these perivascular areas a pseudosystemic disease is produced.

3. Lymph stasis:—The dilated perivascular lymph spaces and the spaces of Obersteiner were thought by Schmaus to be the primary factor in the degeneration. Through the lymph stasis malnutrition or accumulation of toxins initiated the nerve changes.

4. Nerve cell degeneration:—Changes found in the gray matter, especially in the anterior horn cells and the cells of Clarke's column, have been believed to be the primary cause of the degeneration in the white matter.

5. Myelitis:—The marked degeneration with the picture of an inflammatory process presented in some cords has suggested the theory that the condition may be a myelitis with secondary degeneration.

6. Anemia *per se*:—The thickened vessel walls are believed to produce degeneration through malnutrition because of the poor blood supply. Apart from this the theory has been advanced that the blood condition itself is the cause of the nervous lesions.

7. Toxin:—The toxin theory is the one most widely accepted. Whether there is one or more toxins and what the *modus operandi* of the toxin may be in the production of the lesions in the nervous system, are points still to be agreed on.

Hemorrhagic foci.—Minnich found two groups of lesions in the cord. The first consists of capillary hemorrhages and their result, miliary sclerosis, analogous to retinal hemorrhages. The second group shows a peculiar sort of softening dependent on the influence of the general and the local edema, especially of the posterior column, resulting in lymph stasis.

Bullock, Birulja, Teichmüller, von Voss, Clarke, Homen and Siermerling all found hemorrhages in the cord or meninges but von Voss did not consider that these explained the origin of the system disease; Homen believed them due to the same toxin that produced the degeneration and Siermerling regarded them as agonal. On the other hand, Billings, Russell, Batten and Collier, Reuling and Pfeiffer found no hemorrhages.

Toxins.—The theory that a toxin is the primary factor in the production of the cord lesions in pernicious anemia was first promulgated by Lichtheim.

Billings says "The fact that the brunt of the lesion occurs in that part of the tracts involved, fartherest removed from the trophic centers, where the nerve fibre is least protected by its nutritive cell, is evidence of a toxic cause."

Clarke believed that the apparent relation to vessels might possibly indicate the route of conveyance of a toxin.

Gordon thought that the poison, if it is one, does not necessarily follow the route of the blood vessels as the latter are frequently found intact, or very slightly altered. According to him it follows the route of the nerve fibers within the cord without strict regard, however, to the neurone systems. That toxins spread to the cord directly through nerve fibers is a well established fact as illustrated by tetanus.

White regarded a toxin as the etiologic factor and stated that it may be a toxin which produces hemolysis or it may be one of the results of hemolysis.

Henneberg thought that the pathologic anatomic process consists apparently in a primary acute degeneration of the medullary sheaths; chiefly as disseminated small areas caused by the presence of a toxin. The toxin may be conveyed by the vessels without at first causing vessel changes that are demonstrable, although later vascular changes are seen.

Bramwell makes the following classification with regard to the action of the toxin: (1) it acts entirely on the blood, (2) it acts chiefly on the cord, (3) the anemia precedes the cord symptoms, and (4) the toxin involves the blood and cord at the same time.

Petren, Russell, Batten and Collier, Siemerling and Pfeiffer all regarded the foci in the cord as due to a toxin.

Burr, Nonne, Reuling and Lube also favored the toxin theory and believed the anemia and the cord lesions to be due to a common cause.

Blood vessels and lymph spaces.—Burr rejects the vascular theory because of the rarity with which he found changes in the blood vessels.

Nonne noted wide lymph spaces packed with products of degeneration. The small areas of acute degeneration were always in direct relationship to a vessel. He also noted the relation of degenerated areas to vessels which show terminal periarteritis and, when such is the case, the surrounding lymph spaces are markedly widened.

Bowman states, "the blood vessels are found to be affected in proportion to the degree of interstitial change, being apparently healthy in areas where the nerve elements are solely or chiefly involved and presenting very obvious changes in the more densely degenerated parts with marked interstitial change."

Hughes and Spiller found both the intramedullary and extramedullary blood vessels to have markedly thickened walls; the small intramedullary vessels are thickened not only where the sclerosis is dense but also where the tissue of the cord is normal. The thickening implicates all of the coats.

"It must be therefore that vascular changes may aid in the development of the sclerotic tissue, but degeneration of the nervous tissue may begin before any thickening of the vessel walls is detected; it seems not improbable that some toxic substance in the circulation is the cause of the formation of the sclerosis within the white matter and of the alteration of the vessel walls."

Clarke believes the vessel changes are secondary because they are not evident in regions where the nerve degeneration is slight (and recent) and in the areas of the cord where the only evidence of the disease lies in the presence of a few scattered degenerated fibers. The appearances in some instances suggest some relation to the vessels, as the degeneration often seems to begin in the terminal distribution of the small arteries that run into the cord along the septum between the columns of Goll and the posterior external column.

Henneberg states that in the initial stage, especially in the posterior columns, there is sometimes a definite relation of the lesions to larger vessels. These areas lie at the division of the arteries, especially the arterial interfuniculares. The vessels in the early stage may show little change. In early cases lymph vessel alterations are also lacking.

There is too great a regularity in the localization of the lesions for them to be of strictly vascular origin; further the exemption of the gray matter is against a purely vascular origin.

Schmaus regards lymph stasis as the primary pathologic change, this leading to a widening of the glia meshes. In the perivascular lymph sheaths there is often found a homogenous or granular substance.

Woltman believed that "the appearance of these plaques, not only around the blood vessels but also around some of the larger pyramidal cells, seems additional evidence that lymph stasis is an important factor in the production of these foci."

Riggs, Russell, Batten and Collier, and Camac and Milne all regard the vascular changes as of essential importance in the production of the degeneration in the cord. Burr; Bastianelli and von Voss; Jacob and Moxter; Brown, Langdon and Wolfstein; Putnam and Taylor; Pickett, Taylor and Waterman; Homen; Thompson and Pfeiffer either found no vascular changes or finding them do not consider them of primary significance.

Nerve cell degeneration.—Rothmann found, in a great number of cases, a demonstrable disease of the gray substance and believed that a primary affection of this tissue best explains the entire process of continual degeneration. Minnich; Bowman; von Voss; Boedeker and Juliusberger; Jacob and Moxter; Putnam and Taylor; Bastianelli; Russell, Batten and Collier, and Pfeiffer found no important changes in the gray matter.

Relation of the lesions in the cord to the blood supply.—The relation of the lesions to the arterial distribution in the cord has been a favorite field of speculation for most of the writers on this subject. Various theories have been advanced concerning the manner in which the blood supply influenced the formation of the sclerotic areas. It has been explained on the assumption of increased blood supply thereby bringing the toxin; by a poorer blood supply causing a *locus minoris resistentiæ*; by a hyaline exudate around the vessels causing a degeneration; by changes in the vessel walls themselves thus causing degeneration directly or by making the tissue more susceptible to the toxin, and, finally, by thrombosis of the terminal arteries.

Nonne believes that the degenerated areas were especially in the region of the arterial reticulares posteriores and arterial interfuniculares. He agrees with Minnich that the lesions are in the region of the terminal branches of the small vessels of the periphery.

von Voss observed that the destruction of the nervous tissue was mostly in the region of the connective tissue septa and the blood vessels contained in them.

Boedeker and Juliusberger noted that early in the disease process there were circumscribed areas in the region of the instreaming septum in relation to branches of vessels. In some places there were edematous fibers arranged along the septum. They also found small acute areas giving the picture of a subacute myelitic process standing in close relation to the vessels.

Jacob and Moxter state that the process nearly always begins with the formation of perivascular and periseptal areas, which, partly through confluence and partly through production of secondary degeneration, finally produce "strangförmige" degeneration.

Blood supply.—Marburg noted myelomalacia-like areas usually containing a blood vessel. In some of these areas the central-placed vessel is thickly bordered with fatty granule cells surrounded by wide meshed, sieve-like tissue containing many fat granule cells. He explains the fact of the preponderance of lesions in the cervical and dorsal regions by a greater "supply" of toxin to these parts.

Russell, Batten and Collier state, "that the topographical distribution of the degeneration of the white matter of the cord depends on the vascular distribution, there seems to be little question. The blood supply of the cord is mainly from two sources, the anterior median artery in the anterior median fissure and the peripheral arteries derived from the vessels of the pia. The former supply the anterior horns and the white matter bordering on them and the neck of the posterior horns including Clarke's column, while the latter supply nearly all the rest of the white matter.

"The distribution of the lesions in the white matter is that of the peripheral vessels; the only part played by the vessels is in bringing the toxic material to the areas." They do not believe that the middle dorsal region is most involved because of less blood supply, for the anatomic evidence rather indicated that the lower dorsal and lumbosacral regions are least well supplied with blood.

Putnam and Taylor agree with Russell, Batten and Collier, "that the peculiar and relatively constant distribution of the lesions in the cord depends upon the anatomical arrangement of the pial blood vessels, an idea first advanced for combined lesions by Marie." However, they believe that the areas of the cord most efficiently supplied with blood under normal conditions are likely to suffer first under abnormal conditions.

Pickett quotes the doctrine of Marie that the dorsolateral white matter is involved because of a less copious blood supply.

Homen noted the relation of the lesions to the septa and vessels and a predilection for the distribution of the arteriae interfuniculares and its divisions. The areas found early around a septum or vessel whose wall is thickened and whose perivascular lymph space is dilated sometimes remind one of a "myelitic" lesion.

Camac and Milne observed that the destruction and cavity formation present in their cases corresponded almost entirely to a branch of the anterior spinal artery.

Lurbe found the foci of degeneration (referring especially to the brain) to "bear a definite and distinct relationship to the blood vessels."

Anemia.—Bowman rather "regards the anemia as primary and probably the cause of the changes in the cord." Goebel also looks on the anemia as the causal factor in the production of the cord lesions.

The nerve fiber and sheath and system degeneration.—Bowman states that in the earliest lesions the most obvious alteration is found in the nerve fibers themselves. The degenerative changes are for the most part not strictly limited to definite tracts of long fibers.

Nonne observed that the intramedullary white substance was alone affected by the toxin.

Brown, Langdon, and Wolfstein agree with Burr and others who consider the lesion as a primary system degeneration, that is primary as far as the cord is concerned and distinctly neuronic, but secondary etiologically to some condition superinduced by pernicious anemia.

Rueling believed the lesions are due to a diffuse degeneration affecting certain fiber columns.

J. M. Clarke states, "These changes, though fairly regular and possibly indicating that the fibers of the posterior columns which run the longest course are earliest degenerated, do not exactly map out special tracts, but are somewhat patchy in distribution, often varying at different levels for no obvious reasons."

Barrett found in the brain extreme reaction of the nerve fibers adjacent to the blood vessels.

Thompson states that the axis cylinder undergoes, as a rule, less rapid degeneration than the medullary sheath. It ultimately disappears.

Hassin sums up the spinal cord lesions as regressive changes in the nerve fibers and progressive changes in the glia. The pathologic process is confined only to the long fibers which make up the tracts of Goll, Burdach, the spinocerebellar tracts (especially the direct) and the crossed pyramidal fibers. At an early stage the fibers are "in a condition peculiar to peripheral neuritis."

"As the morbid changes found in subacute cord degeneration and peripheral neuritis are alike it would seem proper to characterize the changes in the former as central neuritis, because the central fibres exhibit changes peculiar to the latter." Hassin refers to Meyer who introduced the term "central neuritis" and hinted at its possible occurrence in subacute cord degeneration and concludes "My present studies seem to sustain the correctness of Meyer's suggestion."

The gray matter.—Bulloch noted abundant hyaline material in the gray substance. He believed the hyaline material had exuded from the blood vessels and surrounded the nervous structure of the cord leading to their destruction. The ganglion cells were converted into granular masses in some instances and in others were represented by hyaline masses the shape of the original ganglion cells. The greatest amount of hyaline was in the region of the blood vessels.

Scagliosi noted that the Nissl bodies had disintergated in nearly all of the pyramidal cells of the cortex. Chromatolysis of the anterior horn cells had occurred. He thinks these changes are due to a lack of oxygen.

Henneberg found the ganglion cells of the upper dorsal region to be diminished in number and partly sclerotic. The Marchi stain showed the anterior horn cells to be sometimes completely filled with black masses. There was a diminution of the cells in Clarke's column.

Billings observed in one case that the cells of Clarke's nucleus were small and much decreased in number. The cells of the lateral horn showed disintegration of the Nissl bodies.

Preobrajensky noted that the cells of the anterior horn were edematous and that chromatolysis, especially peripheral, had taken place. There was staining of the achromatic substances and the contour of the nuclei indistinct. In the cortical pyramidal cells stained by the Marchi method there was seen a great number of fine, black, round bodies found chiefly in the periphery of the cell; at times scattered throughout.

Bramwell states that many of the nerve cells of the anterior horn in the dorsal, lumbar, and cervical regions, and the cells in Clarke's column were degenerated.

Barrett found that a number of pyramidal cells in the brain cortex showed the axonal type of cell change.

Types of lesions.—Minnich reported a symmetrical degeneration of a part of Goll's column and a patchy degeneration in the middle root zones.

Bowman states that the minute changes suggest that the process is rather parenchymatous than interstitial in character, at least primarily.

Boedeker and Juliusberger noted two distinct histologic pictures, the acute degenerative process in the nerve fibers, and the reaction on the part of the connective tissue in the form of sclerosis.

Jacob and Moxter noted three types of alteration in the white substance of the cord, (1) pure "strangförmige," (2) pure "herdförmige," and (3) mixed "herd" and "strangförmige."

Russell, Batten and Collier state, "there were obviously two distinct processes at work in relation to the alteration found in the spinal cord in these cases.

"1. A focal destructive lesion. The earliest process consists in a swelling of the medullary sheaths, the axis cylinders remain apparently unaltered. There next occurs a fatty degeneration of the sheath and this in turn is absorbed and at the same time the axis cylinders disappear, a space being thus formed surrounded by the connective tissue of the cord.

"2. A system lesion. The long tracts of the cord exhibit a degeneration similar to that found after transverse lesions of the cord, that is, there is degeneration of the medullary sheaths and axis cylinders and a gradual replacement by connective tissue giving rise to definite sclerosis."

Billings states that two processes are often seen side by side; the one apparently chronic with a tendency to neuroglia proliferation; the other, acute and sometimes very extensive.

Preobrajensky observed two kinds of areas in the white substance of the cord, medulla oblongata and cerebellum, the miliary areas found along the vessels and the areas of destruction of the nerve tissue.

Grinker states that the processes of vacuolation and neuroglia formation were found side by side in nearly all the sections examined.

MICROSCOPIC FINDINGS IN THIRTEEN CASES

The material used in this study was mostly fixed in formalin, although some blocks were fixed also in Zenker's fluid and in alcohol, Weigert's, Marchi's, Bielschowsky's, thinonin, hematoxylin-eosin, Van Gieson's, lichtgrünfuchsin and an elastic tissue stain, were used in all cases except when the only material available consisted in sections taken at various levels of the cord.

CASE N 10

Weigert's stain: First lumbar.—Pathologic changes are limited to the posterior columns. The changes are somewhat patchy and consist in small areas of sclerosis together with scattered groups of dilated sheaths. The changes are more in the central part of the posterior columns. One of the areas showing no sheaths is in apparent relation to a pial vessel.

Ninth dorsal.—The degeneration is still somewhat diffuse.

Fourth dorsal.—The degeneration is rather diffuse in the posterior columns and there is some tendency towards involvement of an area on either side of the central part of the median fissure. There are a few ballooned fibers in the pyramidal tracts. The root zones are slightly if any diseased.

Eighth cervical.—The degeneration is most marked along the posterior median fissure and in the central parts of the posterior columns. There is considerable ballooning of sheaths, mostly in the lateral part of the posterior columns. Some of the peripheral areas seem to be at terminations of the pial arteries.

Fifth cervical.—Both old and recent degeneration are seen in the posterior columns. There is an area of old sclerosis along the median fissure in its central part; this area has intact sheaths scattered through it. Lateral to this is a strip of more or less normal tissue; the sheaths immediately adjoining the posterior median septum appear to be fairly normal, but in one column of Burdach there is an area of old sclerosis running parallel with the posterior median fissure in its central part; also, there are several small areas of sclerosis on this side; several areas near the periphery are possibly in relation to a vessel or septum; scattered through both columns of Burdach are numerous ballooned sheaths. A few sheaths are undergoing alteration in the lateral column. Sections from this cord, as from others, show an unstained area, apparently a ballooned sheath with the axon destroyed, surrounded by normal sheaths that appear to be somewhat pressed together.

Marchi's stain.—In the dorsal regions black dots are seen along vessels in the posterior horn and to some extent along the posterior median fissure in the areas of degeneration in the posterior columns. There are a few fat granule cells in the sclerotic patches. The cells of Clarke's column especially are dotted with black granules.

General histology.—In the less densely sclerotic areas are numerous protoplasmic glia cells with ramifying processes.

The blood vessels in the gray matter are thickened and the lumen of several of the smaller vessels is almost obliterated.

Myelin sheaths in the posterior columns are in various stages of disintegration. The perivascular spaces are not particularly widened, although a few are observed which are filled with glial elements.

In the lower dorsal and upper lumbar regions a few corpora amylacea are seen, more along the posterior median fissure. In the cells of Clarke's column there is a peripheral arrangement of the chromatin substance; the nucleus is frequently absent; some of the nuclei are swollen and irregular; the pericellular lymph spaces are widened. The glia cells are much increased in Clarke's column. The anterior horn cells show definite change in cyto-architecture. Corpora amylacea are seen along vessels and in relation to degenerating ganglion cells.

This section shows definite and extensive involvement of the gray matter.

Cervical.—The anterior horn cells of all groups seem to be altered, those of the external lateral group perhaps more than those of the other groups.

CASE N 35

Weigert's stain: Midlumbar region.—The posterior columns are rather densely sclerosed in areas on either side of the posterior two-thirds of the median fissure with the exception of a border of intact sheaths along the fissure. Lateral to the denser sclerosis is an area of sieve-like structure which extends nearly to the posterior horns.

Throughout the sclerotic area are sheaths that are normal or slightly changed. Just posterior to the central part of the commissure is a small patch of sclerosis with a vessel near the center.

The pyramidal tracts show the densest sclerosis at the outer part. Sheaths, more or less intact, are seen throughout the sclerotic area.

In the anterior white matter are several areas near the periphery and along the anterior fissure in which the medullary sheaths are swollen.

Eleventh dorsal.—Dense sclerosis is found in the column of Goll and at the preiphery of the posterior columns involving also the root entrance zone. The crossed pyramidal tract still shows rather marked sclerosis, but more of the sheaths are ballooned than in lower levels. The cerebellar tracts contain many edematous sheaths. The degeneration in the anterior columns extends along the periphery and on either side of the fissure; the fibers lateral to the dense sclerosis are swollen.

First dorsal.—Old sclerosis is found in a triangular area in the posterior columns, the apex at the middle of the posterior median fissure and the base at the periphery. Around the periphery of the posterior columns is no trace of medullary sheaths. The sclerosis shades out upward and laterally with many normal sheaths scattered through. There is almost complete loss of fibers in the outer part of the cerebellar tracts. The degeneration in the anterior columns is more of a reticulated character. There are several streaks of degeneration extending in from the periphery.

Lower medulla.—Old sclerosis is found in the columns of Goll and Burdach and in the cerebellar tract and patchy, sieve-form degeneration in both pyramidal tracts.

General histology.—There are definite changes in many of the anterior horn cells of Clarke's column. In the dorsal cord many corpora amylacea are seen scattered through the posterior and lateral columns, around vessels, at root entrance zone, at periphery of posterior columns and along septa.

Modified glia cells are numerous; glia nuclei of various sizes and with varying amounts of protoplasm are to be seen. Glia nuclei are especially numerous around blood vessels. "Gitterzellen" are more numerous in the posterior columns and large spider cells are more apparent in the pyramidal tracts.

In the more recent areas myelin sheaths are seen in all stages of disintegration; the glia meshes enclose edematous sheaths, corpora amylacea, and fat granule cells.

The anterior spinal vessels have thickened walls; in the dorsal regions of the posterior columns is an increase of nuclei in the adventitia. Widened perivascular lymph spaces contain many "Gitterzellen."

The meninges are somewhat thickened.

CASE N 45

The only tissue available was a section of cord from the middorsal region.

Weigert's stain.—The lesions are somewhat patchy in one posterior column; in the other they consist of a single area which seems to be in relation to a vessel and a few ballooned sheaths scattered through the posterior columns.

The vessels that are in relation to hyaline-like areas do not have obliterated lumens but apparently have thickened walls; the swollen sheaths are not especially in relation to these patches. Some intact sheaths are scattered through the areas. The areas are more in Burdach's than in Goll's column.

There are several hemorrhages, one in the anterior horn and one in the posterior column.

The pericellular lymph spaces are much enlarged. The vessels in both the cord and meninges are engorged with blood.

A few ballooned sheaths are scattered through the lateral columns.

Marchi's stain.—Many black dots are seen on the pyramidal tracts; in the posterior columns are collections of black masses around the blood vessels.

CASE N 46

Weigert's stain: First lumbar.—There is marked posterior and lateral involvement and moderate anterior degeneration. The posterior columns show an area of normal tissue on either side of the median fissure; lateral to this in the middle third is an area of older sclerosis with intact sheaths scattered through it; in the rest of the posterior columns, except for a border of normal sheaths along the gray matter and periphery, are seen many ballooned sheaths staining with varying intensity; in one posterior column an area of older sclerosis is somewhat centrally located.

Eighth dorsal.—The posterior columns contain an area of dense sclerosis somewhat "V" shaped. Outside of this area are many ballooned sheaths occupying most of the column of Burdach and the peripheral part of Goll's columns. Many reticulated bodies are seen in the sieve-like area corresponding to the size of the glia meshes. They are extremely numerous in this area. Scattered through the sclerotic areas are normal appearing sheaths. The vessel in the posterior median fissure is engorged and thickened but the tissue on either side of the peripheral part is fairly intact.

The lateral change is limited to the pyramidal tracts and like the change in the anterior columns consists in ballooning of the sheaths.

Seventh dorsal.—The sclerosis in the posterior columns is far advanced and consists of an area of dense sclerosis along the median fissure, triangular in shape and extending from the upper part of the fissure and including most of the periphery; lateral to this is more recent degeneration; the posterior root entrance zone is degenerated. The change in the lateral columns is extensive, but more recent. In the anterior columns on either side of the peripheral part of the median fissure, is a patch of old sclerosis surrounded by ballooned fibers. There is a hemorrhage in the posterior column at the edge of the most marked sclerosis. The smaller vessels in the sclerotic area have thickened walls and are engorged with blood. On the other hand, areas with little or no change show vascular involvement. The meningeal vessels are thickened.

Fifth dorsal.—The lesions are similar to those of the seventh dorsal except for slight variations in extent and degree of sclerosis.

Cervical.—The old sclerosis is much less extensive than in the dorsal: it occupies a wedge-shaped area on either side of the peripheral half of the median fissure. Lateral to this is considerable normal tissue with ballooned sheaths and patches of older degeneration scattered through it. There are also several areas of sclerosis at the periphery, possibly in relation to the pial vessels.

The change in the lateral columns extends to the periphery and includes both cerebellar paths; the sheaths are dilated. There is also fairly well marked change anteriorly with some sclerotic tissue and a border of ballooned fibers on either side of the median fissure. The root entrance zone is decidedly degenerated on one side.

Marchi's stain.—The lower levels show degeneration throughout most of the posterior columns, at least in the central part of each column. In the higher levels the changes are more peripheral and extend slightly into the central part.

General histology: First lumbar.—The anterior spinal vessels show rather marked thickening of the adventitia. The blood vessels in the white matter generally and in the posterior columns particularly are definitely involved.

In the areolar areas of degeneration many modified glial cells are seen in the posterior, lateral, and anterior columns. The areas are especially marked in the lateral columns.

Seventh dorsal.—In the posterior columns the glia cells are very numerous. There is a moderate number of reticulated cells; the nuclei of these cells are in various stages of disintegration. Many of the glial meshes are occupied by "Gitterzellen," others appear to be empty. In the denser parts the vessels show some hyalinization of the walls; in the less dense areas of degeneration the adventitia is thickened. In most of this area the perivascular lymph spaces are markedly filled with cellular elements. While the fat granule cells are fairly numerous in most of the sclerotic areas they are especially numerous in the somewhat less densely sclerosed areas, and the nuclei are usually more distinct. A few appear to contain amyloid bodies. In the more areolar portions many protoplasmic glia cells with long branching processes are seen. In the sclerotic areas the blood vessels stand out more distinctly. The vessels in the gray matter appear somewhat enlarged and some of them are engorged with blood. The nuclei of the ganglion cells seem to be normal but about half the cells give an abnormal staining reaction.

Upper dorsal.—Masses of fat granule cells are seen in the center of the posterior columns; with Weigert's stain these areas appeared as dense sclerosis. In the lateral columns there are more spider cells.

Cervical.—The anterior horn cells are fairly normal, but there is considerable widening of the pericellular spaces. There is an increase in the number and size of the glia cells in the gray matter. Many modified glia cells are seen in the posterior and lateral columns. The blood vessels are thickened and their dilated perivascular spaces contain many cellular elements. There is no special tissue reaction around the vessels.

These sections show fairly definitely the greater ballooning of the fibers in the upper portions of the pyramidal tracts and the more complete destruction of the sheaths and axons lower in the cord. The reverse seems true in the afferent tracts.

In this cord is the picture of a fat granule cell myelitis of the white matter. The areas which appear to be densely sclerotic in the Weigert sections are seen to be made up largely of masses of granule cells occupying the glial meshes.

This cord shows especially distinctly the various stages of myelin sheath and axon involvement.

CASE N 49

Weigert's stain: First lumbar.—There are well defined areas of sclerosis in the posterior and lateral columns. The area in the lateral columns shows few ballooned sheaths. In the posterior column the central part of each posterior column is fairly densely sclerosed with ballooned sheaths, especially at margins.

Eighth dorsal.—In the posterior columns is a V-shaped area of fairly dense sclerosis with the apex at the upper third of the posterior median fissure; many sheaths of fairly normal appearance are seen in the sclerotic portion; ballooned sheaths are scattered through the rest of the posterior columns. In the upper part of Burdach's column is an area resembling the dense central area that is in apparent relation to a patent blood vessel and has many normal appearing sheaths in it.

First dorsal.—The old degeneration in the posterior columns is more definitely circumscribed. It is triangular with the apex at the commissure and the base about one-sixth the length of the fissure from the periphery; there are several areas of ballooned fibers, one well defined area being in Lissauer's zone.

In the lateral columns is fairly well marked sclerosis with some swollen sheaths outside the area of denser sclerosis.

The anterior columns are probably degenerated on either side of the median fissure.

Fourth cervical.—The involvement in the posterior columns consists in a somewhat V-shaped area of dense sclerosis on either side of the posterior median fissure and joining at the middle half of the fissure, it contains a number of intact sheaths; scattered through the posterior columns are a number of areas apparently surrounding a vessel and containing some intact or thinned medullary sheaths.

The lateral columns present many ballooned sheaths giving a sieve-like appearance; there are a few swollen sheaths in the anterior columns. The anterior cerebellar tracts are apparently densely sclerosed.

First cervical.—The area of old sclerosis in the posterior column curves outward from the upper third of the median fissure around the periphery to the posterior horns; there is a strip of nearly normal sheaths between this area and a streak of less dense sclerosis containing many sheaths running on either side of the posterior median septa.

The pyramidal tracts contain little or no dense sclerosis; there is some sclerosis in the cerebellar tracts (Fig. 139).

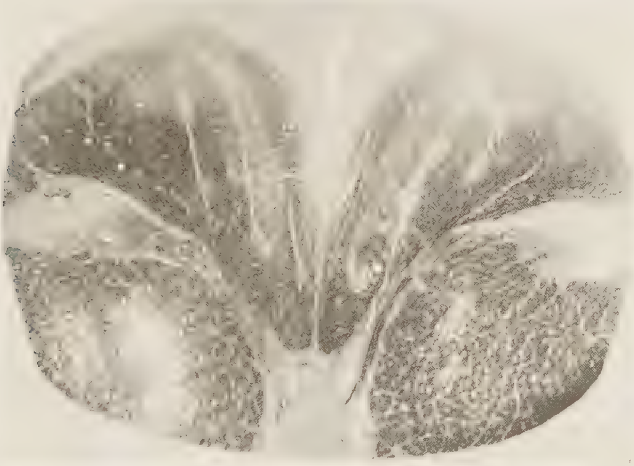


FIG. 139 (Case N 49).—Posterior column of the first cervical segment of the spinal cord. (Weigert.)

Marchi's stain: Middorsal.—Black masses are collected around the small vessels and elsewhere on either side of the posterior median fissure; there is marked degeneration in the pyramidal tracts, but not in the other lateral tracts.

Bielschowsky's stain.—Various swollen and tortuous fibers are noted.

General histology: Lower dorsal.—On either side of the anterior median fissure near the commissure are a few corpora amylacea in an area with a few ballooned sheaths. There is a moderate increase of the glia cells. The blood vessels are slightly changed.

In the posterior columns are many corpora amylacea, especially at the periphery and in the posterior root entrance zone. Few ballooned sheaths are seen. The blood vessels are nearly normal. In the more reticulated areas many protoplasmic glia cells but almost no fat granule cells are seen.

In the lateral columns is a moderate amount of sieve-like structure. In the more central part is a rather large dense area of sclerosis with very few corpora amylacea. The area of more advanced sclerosis contains many glia nuclei. Many fat granule cells are seen.

Middorsal.—Many corpora amylacea are seen, especially in the posterior third of the posterior columns. The long sections show many corpora amylacea, sometimes several in a row. Protoplasmic glia cells are extremely numerous in the lateral columns; often several are seen more or less in rows. An occasional myelophage is seen. Some of the corpora amylacea appear to have a granular center. The blood vessels show slight changes.

Lower medulla.—In the posterior columns many small and moderate sized glia cells are seen, especially in Burdach's column. In Goll's column are some axons which stain very indistinctly; practically no sheaths remain.

In the pyramidal tracts are a considerable number of spider cells and some fat granule cells. There is an increase in glial fibrils. A large number of sheaths and axons is gone. A few corpora amylacea are seen. In the central part is a markedly reticulated area. The vessels present slight changes. Ballooned sheaths are scattered through the tract; the axon is often pushed to one side. Another similar area is seen somewhat more centrally.

CASE N 71

Weigert's stain: Fourth sacral.—There is possibly some change in the pyramidal tracts and the large posterior root bundle fibres appear thin and pale.

Second sacral.—The section is probably negative except for the paler staining area laterally and the alterations in the fibers of the posterior root bundle.

Third lumbar.—A rather dense patch of sclerosis in the center of the posterior columns is somewhat diffuse and of some duration of time; sheaths that appear to be normal or but slightly involved are scattered through the sclerosis in the posterior columns; there are practically no ballooned fibers.

In the lateral columns is a well marked area of degeneration somewhat triangular in shape with the base at the periphery. The part of the periphery anterior to this area is pale-staining, but there is no definite degeneration.

Second lumbar.—There is marked degeneration of the lateral area and fairly marked degeneration of the posterior column. The lateral area is still wedge-shaped. The posterior column involvement is somewhat more circumscribed but still has a number of more or less intact sheaths scattered through it, especially in the outer parts of the area.

First lumbar.—The degeneration is well marked in the posterior and lateral columns. There is a somewhat diffuse well marked patch in both posterior columns midway dorsoventrally, but nearer the median fissure. Both anterior and posterior roots appear to be degenerated.

Upper dorsal.—Old degeneration in the lateral columns is well marked at the periphery, but centrally towards the apex of the area more and more intact sheaths are seen. In the posterior columns the degeneration is somewhat diffuse and patchy and involves the column of Goll more than Burdach's column; on one side particularly the sclerosis extends well into the funiculus cuneatus.

The relation of the areas in the posterior columns to the vessels is indefinite; the vessels appear to be thickened in both the posterior columns and in the gray matter but they do not seem especially more involved in the sclerotic areas than in the gray matter, except for a vessel near the center of a sclerotic patch in the posterior columns. Longitudinal sections show a peculiar anatomic distortion in the lumbar region.

Marchi's stain.—Cells of the anterior horn and of Clarke's column are markedly pigmented with fine granules; in some of the cells the nucleus is likewise involved; sometimes the Marchi dots are fairly well limited to the poles of the cells. In the lower thoracic region is definite degeneration in the roots.

General histology.—Many glia cells are observed in all the areas. The ganglion cells show various stages of chromatolysis; in some the chromatin substance in the nucleus is arranged in masses around the periphery of the nucleus; in others no nucleus is seen and the cell is diffusely stained.

A hematoxylin-eosin section of the lower medulla shows swollen medullary sheaths in the cerebellar tracts. The cells of the nucleus gracilis and nucleus cuneatus are diffusely stained throughout and show other chromalytic changes. The glia cells are markedly increased in the posterior area. The pyramidal tract also shows an excess of glia cells with varying amounts of protoplasm. The vessels in this region appear to have a hyaline exudate around them.

The peripheral nerve (sciatic) shows many black dots with the Marchi stain. The Weigert sections show less definite degeneration.

CASE N 100

Weigert's stain: Sacral cord.—No changes are observed.

Lumbar region: Second lumbar.—In the central part of one posterior column is a number of ballooned sheaths with little evidence of sclerosis. In the other posterior column in the central part are a few dilated sheaths.

Dorsal region: Eleventh dorsal.—Patches somewhat similar to those seen in the lumbar region are observed, but they are slightly less extensive.

Middorsal region.—No definite involvement of the posterior columns is observed, but peripherally in one lateral column is a small patch of sclerosis.

Marchi's stain.—There is an excess of pigment in the anterior horn cells.

General histology: Lumbar region.—At the periphery of the posterior columns are many corpora amylacea. An area of swollen sheaths is seen in the central part of the posterior median septum. The tissue surrounding a cross section of a vessel in the posterior median septum has been separated from the vessel by an extravasation, possibly a hemorrhage. Hyaline degeneration has occurred in some of the smaller vessels in the posterior columns.

Lower dorsal.—Few corpora amylacea and an increased number of glia cells are seen on longitudinal section.

Middorsal.—The corpora amylacea are more numerous at the root entrance zones. There are a few dilated sheaths in the posterior columns. The cells of Clarke's column show chromalytic changes.

CASE N 118

Weigert's Stain: Fifth lumbar.—Except for a slight degeneration laterally and a questionable change in the roots the section is negative.

Second lumbar.—Definite, although not extensive, change is observed laterally and posteriorly. The lateral columns are lighter staining and show slight sclerosis; the medullary sheaths are slightly swollen. The involvement of the posterior columns is somewhat diffuse and consists in groups of ballooned sheaths, which may have some relationship to the vessels.

First lumbar.—Well marked changes are observed in the posterior and lateral columns; the posterior columns show extensive ballooning of the sheaths, especially in the central parts of the columns; intact sheaths are seen in relation to the involved sheaths and scattered through what appears to be old sclerosis. There are no changes in the area adjoining the posterior horns. Both the anterior and posterior roots appear to be diseased (Fig. 140).

Seventh dorsal.—The lateral columns show extensive ballooning of the fibers fairly well limited to the pyramidal tracts; the cerebellar tracts are not involved. The degeneration in the posterior columns is patchy and consists of dense sclerotic areas in the region of the median fissure and of groups of ballooned fibers in Burdach's column with some sclerotic tissue. There is a questionable small hemorrhage in the margin of one of the patches. Just posterior to the commissure is a blood vessel with a moderately thickened wall, surrounded by a small area of sclerosis containing some intact sheaths; the sheaths outside the area are normal in appearance (Fig. 141).

Third dorsal.—The degeneration is more marked and more diffuse both posteriorly and laterally than in the seventh dorsal. The degeneration in the lateral columns is recent and consists mostly of ballooned sheaths. The changes in the posterior column are older. There are areas of degeneration in each column of Goll and of Burdach which are separated to some extent by a more nearly normal area; the area near the median fissure is the older. Lissauer's zone probably is diseased.

Lower medulla.— There is extensive recent involvement in the spinocerebellar tract and fasciculus cuneatus.

Marchi Stain: Fifth lumbar.—Degeneration is well marked in the posterior columns in the central parts and along the periphery, also in the lateral columns. Black masses are grouped along the vessels. The roots are distinctly degenerated. The anterior horn cells are strikingly pigmented.

Upper dorsal.—In the pyramidal tract and around a central area of sieve-like degeneration the medullary sheaths are shown to be degenerated. The anterior and posterior roots are still clearly diseased.

Cervical.—Fatty granule cells are seen in the posterior columns.

Medulla.—The cerebellar tracts are extensively involved. Burdach's column also shows evidence of recent degeneration. The cells of the nucleus gracilis contain an excess of pigment granules.

Medulla.—(Section through the twelfth nucleus) Degeneration is found in the corpus restiforme and in the pyramidal tracts.

Pons.—Marchi dots are seen in the brachium conjunctivum.

General histology.—In the middorsal region many corpora amylacea are seen in the posterior columns, also many glia cells. The blood vessels are not especially involved. There is some chromatolysis in the cells of the anterior horn and of Clarke's column. A few "Gitterzellen" are found in the posterior and lateral columns, and a number of spider cells in the lateral columns. Longitudinal sections of the dorsal cord stained with hematoxylin and eosin show rows of corpora

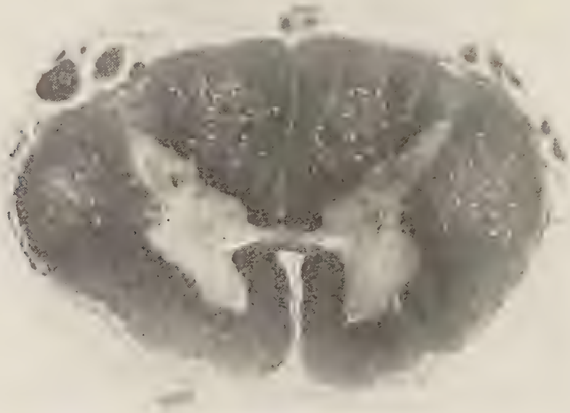


Fig. 140 (Case N 118).—First lumbar segment of the spinal cord. (Weigert.)

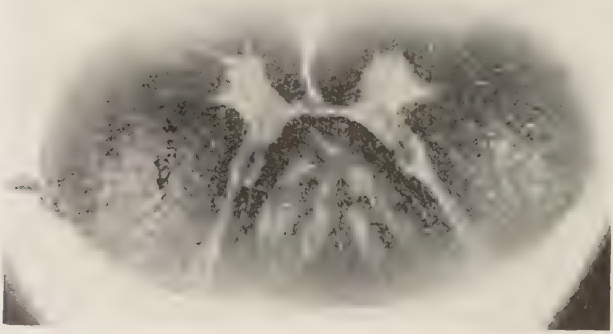


Fig. 141 (Case N 118).—Seventh dorsal segment of the spinal cord. (Weigert.)

amylacea and fat granule cells in the posterior columns, especially Burdach's. In the cervical region is also an increase in glia cells in the posterior columns and to a less extent in the lateral columns.

Lower dorsal.—Many corpora amylacea are found at the posterior root entrance zones; they are more numerous in the central and lateral parts of the posterior columns. On longitudinal section they are found to be more or less in rows, around blood vessels, and at the periphery. Thionin and kresyl violet stains show rather marked chromatolysis in the cells of the anterior horn and Clarke's column. In a vessel in the anterior horn there is a clump of bacteria.

Heidenhain's iron hematoxylin shows many corpora amylacea along the vessels and septa in the lateral column as well as scattered through the sieve-like area, also in the posterior columns and posterior horns at the periphery. There is a considerable number of "Spinnenzellen" in the lateral columns. The wide meshed glial spaces and swollen sheaths in various stages of disintegration are clearly seen in the lateral columns, the same is true of the axons although apparently in them the changes are later than in the sheaths. Some of the vessels in the posterior and lateral columns are thickened but are not in definite relation to the areas of sclerosis.

The lymph spaces around the vessels in the posterior and lateral columns are dilated and contain cellular elements. The spider cells are more numerous in the reticulated areas.

In the gray matter of the dorsal cord the perivascular and pericellular lymph spaces are widened.

The peripheral nerves are definitely involved.

CASE N 123.

Weigert's stain.—This cord presents a rather clearly circumscribed area of degeneration beginning in the central part of the posterior columns in the upper thoracic region and approaching the posterior median groove until in the upper thoracic and cervical regions the sclerotic area is V shaped. This degeneration extends into the medulla oblongata in the column of Goll. The anterior roots, and to a less extent, the posterior roots are degenerated (Figs. 142 and 143).

Marchi's stain.—In the lower dorsal regions a rather small area of dense sclerosis is surrounded by ballooned sheaths. In the reticulated portions of the area are many Marchi dots. There is an excess of black granules in the cells of Clarke's column.

The middorsal cord shows very little evidence of degeneration. In the upper levels of the cord the dots are mostly at the margin of the area of sclerosis.

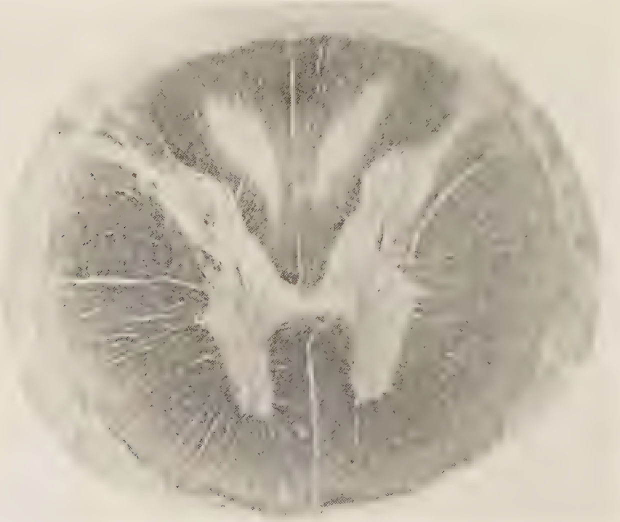


Fig. 142 (Case N 123).—Twelfth dorsal segment of the spinal cord. (Weigert.)

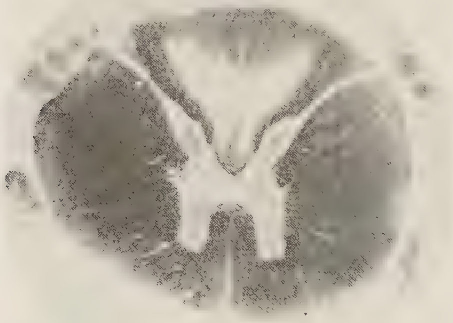


Fig. 143 (Case N 123).—Seventh dorsal segment of the spinal cord. (Weigert.)

There is a definite degeneration in the posterior columns in the region of the posterior root entrance zone.

Ford Robertson's stain.—Swelling and slight varicosities of the axons are seen.

Bielschowsky's stain.—The axons are seen to be decidedly nodular.

General histology.—The changes in the cells of the anterior horn and Clarke's column are well marked. The chromatin substance is frequently arranged in irregular masses at the periphery of the cell. The nucleus is absent or in various stages of disintegration. In some of the cells the center is filled with pigment.

In the lower medulla there is extensive sclerosis in Goll's column and to a much less extent in Burdach's. Large protoplasmic glia cells are seen. There are more corpora amylacea in Goll's column. The cells of the nucleus gracilis show definite tigrolysis.

In the dorsal regions the glia cells are very much increased in the diseased portion of the cord.

The blood vessels show definite hyalinization, especially in the old sclerotic areas.

CASE N 125

Weigert's stain.—There are no marked changes in any part of the cord; there is possibly a slight pallor in the posterior column.

General histology.—A few corpora amylacea are seen along the vessels and in the lateral part of the posterior columns, also in the lateral columns. The most marked increase of the corpora amylacea is seen in the posterior root entrance zone or Lissauer's zone; this is constant in the dorsal sections. The pericellular lymph spaces are widened, especially in Clarke's column. The glia cells are increased in size and number in the posterior columns, and in the lighter areas in the Weigert sections there is possibly a slight swelling of the myelin sheath.

The cells of Clarke's column show definite chromatolysis; the changes in the anterior horn cells are slightly less marked. The nucleus is often partly or entirely disintegrated and the chromatin substance arranged in irregular masses around the periphery of the cell.

Bielschowsky's stain.—Some of the fibers in the posterior columns appear to be nodulated.

CASE N 127

Weigert's stain: First lumbar.—There is marked degeneration in the lateral and posterior columns. In the posterior columns the involvement is extensive, in the central part, and more recent in the lateral parts. The sheaths on either side of the lower two-thirds of the median fissure and bordering on the gray matter are intact.

The sclerosis in the lateral columns is older and has many fairly normal sheaths scattered through it.

Eleventh dorsal.—The changes are similar to those observed in the first lumbar, but the area in the posterior columns is slightly more circumscribed. There are a few ballooned fibers in the anterior column along the anterior median septum.

Seventh dorsal.—There is marked sclerosis of all the posterior column except a small V at the end of the posterior median fissure and a narrow border of normal or ballooned sheaths along the posterior horns. As a whole the sclerosis is most marked next to the median fissure and about the center of the fissure. The changes in the column of Burdach are more recent.

In the lateral columns are fairly marked sclerosis in the pyramidal tracts and recent degeneration in the cerebellar tracts. A few groups of ballooned sheaths are seen anteriorly.

Second dorsal.—There is marked sclerosis in the posterior columns, especially in the column of Goll; there is a small V shaped area of fairly normal fibers at the extreme periphery of the posterior columns; many sheaths in the lateral part of the posterior columns are ballooned.

Eighth cervical.—Degeneration of all of the posterior columns is marked, except a band along the posterior horns in which considerable ballooning of sheaths is noted, especially toward the periphery. The sclerosis in the pyramidal tracts is not so dense as in the lower levels; there is well marked degeneration along the anterior median fissure.

The longitudinal sections show sheaths in various stages of disintegration in the areas involved.

Marchi's stain.—In the lumbar region are many fat granule cells, especially near the median fissure.

Dorsal.—There are many fat granule cells in the lateral columns as well as in the posterior columns.

Ford Robertson.—Various changes in the axon are observed; the fiber is apparently early involved but is not entirely destroyed until the sclerosis is well advanced.

General histology.—There is marked chromatolysis of the anterior horn cells in the upper lumbar region.

In the dorsal regions the cells of the anterior horn and Clarke's column show definite changes various degrees of chromatolysis and staining of the achromatin substance.

Spider cells are very numerous in the sieve-like areas, especially in the lateral columns. Many fat granule cells are found in the lateral columns, but they are more numerous in the posterior columns.

Longitudinal sections of these areas show rows of "Gitterzellen," some of mammoth size and containing a double nucleus. The cells often contain very large vacuoles.

Quite a number of corpora amylacea are seen around the vessels in the posterior columns and in the glia meshes. The vessels, especially those in the posterior columns, show thickening of the adventitia, but the vascular changes are not marked as a rule. The anterior horn cells show some fuchsinophile granules but not marked.

In this cord also is found the picture of a fat-granule cell myelitis in the white matter, and with definite changes in the gray matter without extensive vascular involvement. The various changes in the tissues are clearly demonstrated here: the beginning reaction of the medullary sheaths through the stage of enlargement and pale, irregular staining until they finally disappear. The glia cell history is well brought out in these sections; all stages are seen from the early increase of the number and size of the neuroglia through the large protoplasmic glia cell to the stellate spider cell and the fat-granule cell which is so common in this cord up to the stage of dense sclerosis.

CASE N 130

Weigert's stain.—The changes are relatively slight in the Weigert preparations. Isolated islands of degeneration are not seen. In the posterior columns slight changes consist of an obscurely outlined band along either side of the median groove. The change is most marked in the cervical region.

In the lateral columns a somewhat paler staining area is seen; it is most marked at the ninth thoracic segment.

In the upper thoracic cord a peculiar enlargement of one posterior horn near the commissure is to be observed. It is suggestive of the lesions reported by Bäumler, Bullock, and Camac and Milne. However, there is no evidence of cavity formation.

Lissauer's zone appears definitely abnormal but the change is rather diffuse.

Marchi's stain.—The cord appears negative except in the anterior and posterior roots where many Marchi dots are seen.

General histology.—There is decided chromatolysis of the cells of Clarke's column. The anterior horn cells present less evidence of degenerative changes. The pericellular spaces are markedly dilated around the cells of Clarke's column. In the upper part of the cord an occasional sheath in the posterior column is seen to be edematous. The lateral column shows definite involvement of the myelin sheaths, and the neurofibrils are somewhat irregular.

In the lower dorsal region the lateral columns contain many spider cells and corpora amylacea, and a few fat-granule cells. The posterior column in this section shows only a slight increase of glia and very few corpora amylacea.

In the longitudinal sections an occasional row of several protoplasma glia cells is seen; these cells contain large nuclei and some have a marked amount of protoplasm.

There is some swelling of the sheaths and nerve fibers in the posterior root entrance zone.

CASE N 137

Weigert's stain: Mid-dorsal.—In the central part of each posterior column are several patches of sclerosis in apparent relation to vessels or septa. Scattered through the posterior columns, somewhat more in Burdach's column are a number of ballooned sheaths.

The lesion in the lateral columns consists of a well circumscribed reticulated area. There is comparatively little sclerosis in this area.

Marchi's stain.—With this stain degeneration is not seen around the vessels or in the patchy areas in the posterior columns; in the sieve-like areas, especially in the lateral columns many dots and granule cells are seen. The roots are definitely involved.

General histology.—In the posterior columns a few corpora amylacea occupying glia meshes are found. Spider cells are found in the area of ballooned sheaths. The blood vessels show little involvement. In the lateral columns are many fat-granule cells; a number of them show large vacuoles. The medullary sheaths are in all stages of destruction.

The peripheral nerves show some degeneration with the Marchi's stain.

DISCUSSION OF PATHOLOGIC CHANGES

The blood vessels and lymph spaces.—Whether or not the distribution of the vessels is a factor in the location of the lesions it is certain that the sclerosis is not due to changes in the vessel walls. In isolated instances hemorrhages and thrombosis are seen but certainly are not the primary cause of the degeneration.

As the sclerosis advances vascular changes are more likely to be seen. Hyaline degeneration is the most common change. Intimal proliferation occurred relatively infrequently. Thickening of the adventitia with increase of the nuclei in the vessel wall was fairly common. The vessels in relation to the earlier areas not infrequently are normal. The clump of bacteria found in one section was probably the result of a terminal septicemia.

The dilatation of the lymph spaces was a common, but not necessarily constant finding. In the stage in which the "Körnchenzellen" are numerous, the perivascular lymph spaces are usually notably widened and filled with cellular elements. The space of Obersteiner is often dilated around both the anterior horn cells and the cells of Clarke's column. However chromatolysis is often marked in cells with a fairly normal pericellular lymph space. Lymph stasis is probably a factor in the pathogeneses of the cell changes and sclerosis in the white matter, but hardly the primary cause since changes occur in both instances without evident lymph stasis.

Nerve cells.—Changes in the nerve cells have not commonly been looked on as an important part of the findings in subacute combined degeneration. Many writers have referred to various grades of alterations in the anterior horn cells and in the cells of Clarke's column. Our sections showed definite and often marked chromatolysis of the cells of Clarke's column and to a less extent of the anterior horn cells. In cases in which the cord changes were otherwise slight the cells of Clarke's column are distinctly involved (Figs. 144, 145, and 146).

Not infrequently there was staining of the achromatin substance so that the cell appeared more or less uniformly stained; often the cells stained very deeply. The common arrangement of the tigroid substance was in irregular masses around the periphery. These cells often had lost their processes and nucleus.

The earliest change was an eccentric position of the nucleus with an excess of pigment in the cell. The nucleus was apparently gradually extruded or disintegrated. In some sections all stages of cell change were seen, rounded cells without processes, spindle-shaped cells, cells with excess of pigment, cells with abnormalities of the nuclei, dark rather uniformly staning cells, peripheral arrangement of the chromatin substance, and finally cells that were almost unstained appearing as shadows of the former cell.

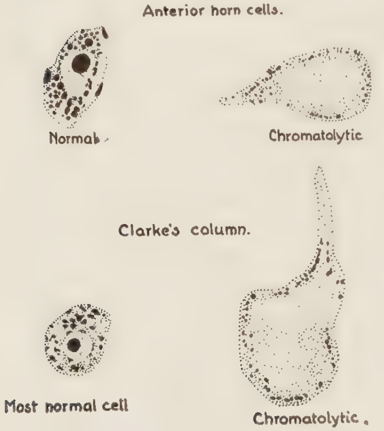


FIG. 144.

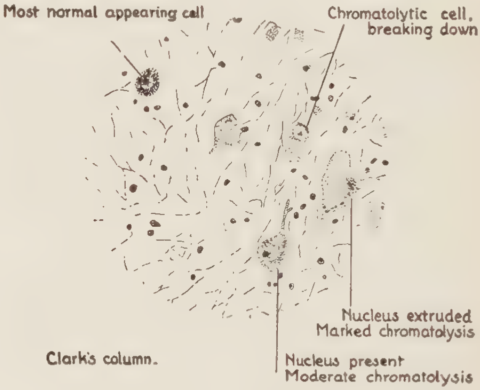
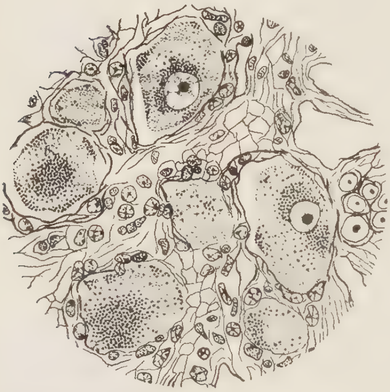
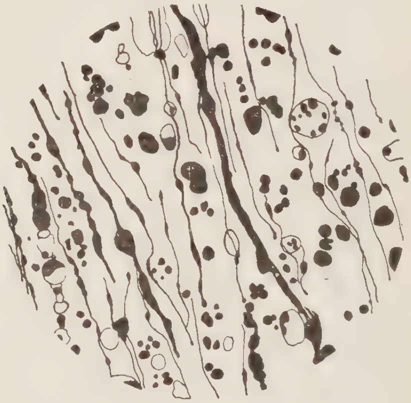


FIG. 145.



Posterior ganglion cells showing pigmentation.

FIG. 146.



Degenerating myelin sheaths.

FIG. 147.

The anterior horn cell changes are not unlike those seen in multiple neuritis. The involvement of the cells of Clarke's column is very definite and constant and seemingly must play some part in the degeneration of the white matter in the cerebellar tracts. The changes in the anterior horn cells are probably due to the involvement of the peripheral nerves which we found to be constant.

7. *Medullary sheath.*—The changes in the myelin sheath are distinctly presented in the various sections from these cords (Fig. 147).

The transverse sections stained by Weigert and Van Gieson show the early swelling of the sheath; the longitudinal sections also show the enlargement of the sheath and the further stage of increasing tortuosity of the sheath. The staining is lighter than normal and becomes definitely irregular.

The medullary sheath gradually becomes thinned out until it has the appearance of dots connected by a fine thread and in a still more advanced stage only a faint ring can be made out. Groups of these ballooned sheaths with the axis cylinder pushed to one side or obliterated and fat granule cells possibly surrounded by the faint line of myelin sheath of a fine glia network make up the sieve-like structure so frequently seen in subacute combined degeneration. The disintegrating myelin is apparently carried through the lymph spaces to the blood vessels by the fat-granule cells.

In the moderately advanced stage the sheath is seen to be more or less broken up and the area filled with fat globules.

In another sort of area where a pale area surrounds a blood vessel the sheaths contained in the patch are either normal or smaller and paler than the other sheaths.

The axon.—The Bielschowsky and Ford Robertson sections seem to indicate an early involvement in the axon (axis cylinder) (Fig. 148). In areas where the myelin sheath is apparently intact the axon may be showing the early changes, incident to degeneration. Pfeiffer found the axis-cylinder process to be well preserved as shown by the Bielschowsky method; in the brain even where there was advanced nerve cell degeneration the neurofibrils were well preserved.

While it is fairly definite that the axons undergo slight changes early in the disease it is certain that the disintegration does not occur so rapidly in it as in the medullary sheaths for axons are found in greater or lesser numbers in areas with extensive myelin sheath involvement. This is well illustrated in a peripheral nerve which showed marked demyelinization by the Weigert method but in which a number of axons were found.

The earliest changes are probably seen in the silver stained longitudinal sections showing slightly swollen and slightly irregular axis cylinders; the neurofibril becomes definitely nodular and tortuous in its course. With the hematoxylin-eosin stain the axis cylinders are seen to be swollen and pale staining; as the swelling of the sheath increases the axon is often found to one side of the ballooned sheath or after the sheath is practically gone the faint staining axis cylinder is sometimes seen in the glia mesh possibly pushed to one side by "Gitterzellen." The axon becomes more granular and varicose and finally is apparently broken up into small particles from which, together with the disintegrated myelin sheath, corpora amylacea are supposed to arise (Homen).

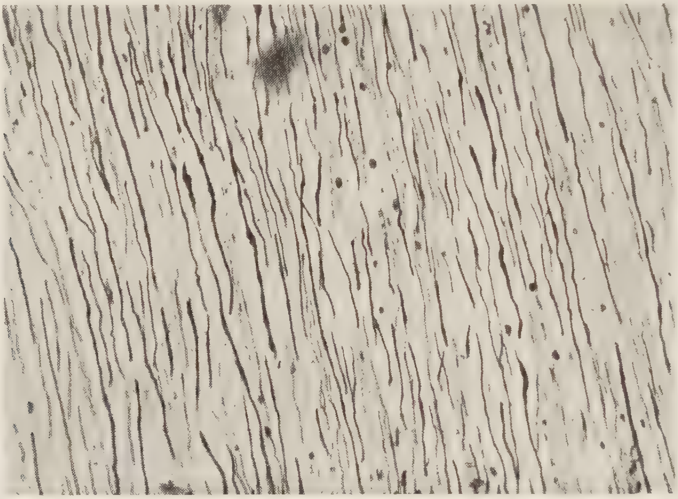


FIG. 148.—Some tendency to irregularities in the fibers. (Bielschowsky.)

The neuroglia.—With this even more than with the other tissue elements the picture in any individual case is apparently modified by the degree of acuteness of the process and probably also by the ability of the tissue to react to the stimulus. The glial elements show a marked sensitiveness to the supposed toxin for even before the fibers are appreciably affected there is an increase in the size and number of glia cells. It is not evident that the neuroglia proliferation initiates the parenchymal changes but rather progresses *pari passu* with the alterations in the nerve fiber.

There is an increase in the protoplasm of the glia cell and the

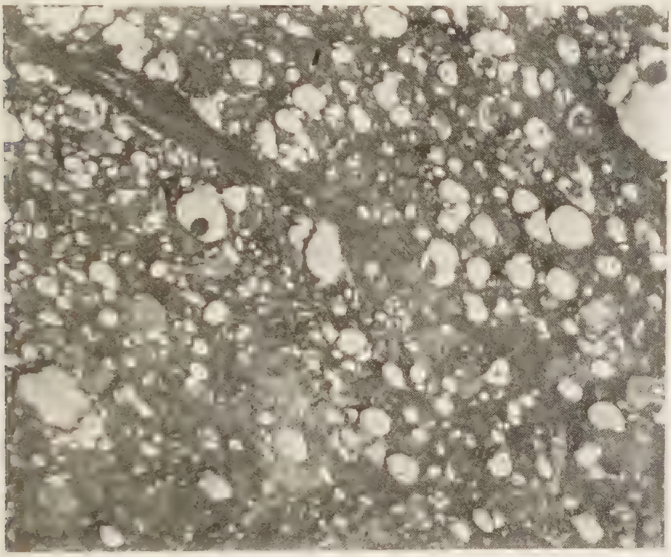


FIG. 149 (Case N 137).—Sixth dorsal segment of the spinal cord. Large numbers of fat granule cells in the glia meshes. (Iron hematoxylin.)

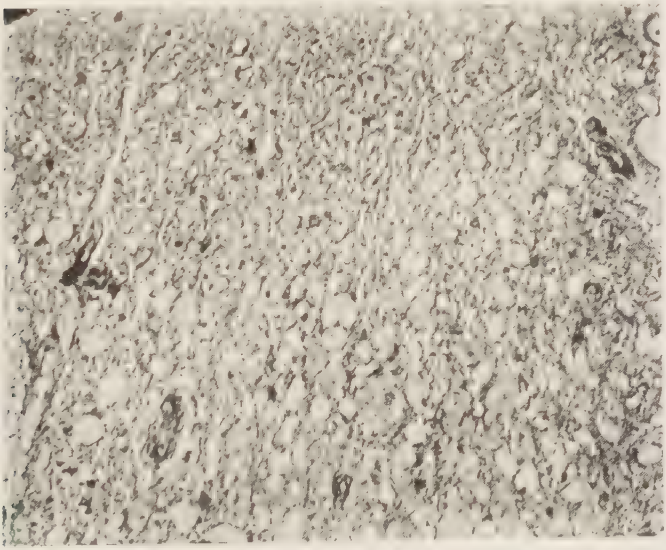
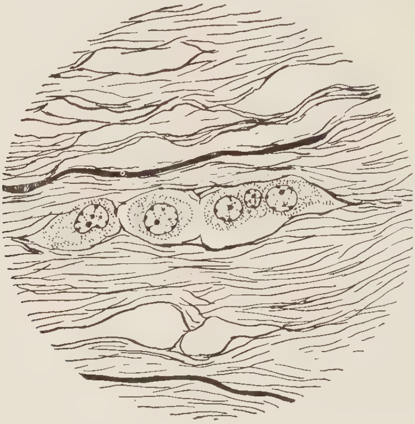


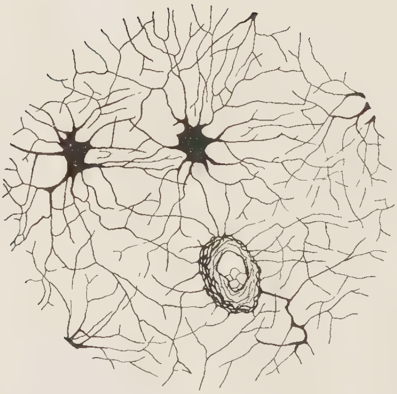
FIG. 150 (Case N 127).—Middorsal region; posterior column of the spinal cord. Fat granule cells occupying the glia meshes and spaces in the ballooned sheaths. (*Lichtgrünfuchsin.*)

nucleus stains very distinctly. As the ballooning of the sheath takes place the large protoplasmic glia cells form processes that surround the disintegrating fiber. At this stage the Weigert stain shows swollen medullary sheaths and a little later the characteristic sieve-like area. These cells vary greatly in size and not infrequently they present extensive processes which, by apparent anastomosis and interlacing with processes of other glia cells, forms a most beautiful network. The fibrils often show a definite relationship to the vascular structures.



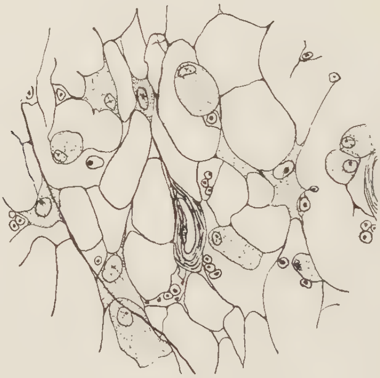
Row of fat granule cells.

FIG. 151.



Cajal glia

FIG. 152.



Posterior column
showing histogenesis of fatty granule cell.

FIG. 153.

As the sclerosis becomes more marked the spider cells are less and less distinctly seen and in place of the large protoplasmic branching glia cells forming a rather loose reticulum we see a mass of fibrils with comparatively few nuclei.

The so-called fat-granule cell or "Gitterzelle" is a very interesting part of the picture and seemingly plays an important, although not primary part in the destruction of the axon. These large protoplasmic cells present a reticulated appearance with the hematoylin stains and a granular appearance when stained with osmic acid. They are often vacuolated. On cross section they are seen lying in glia meshes and on longitudinal sections often appear in columns apparently occupying the space of the disintegrated axon, the fat-granule cell being filled with myelin particles. These neurophages accumulate around the vessels and often form a ring around a vessel filling the adventitial lymph space. In some sections the number of granule cells is so great as possibly to warrant terming the process at that level a "fat-granule cell myelitis." Sometimes areas that appear sclerotic in the Weigert sections are found to be made up of masses of "Gitterzellen" in a glial reticulum. In the late stages the nuclei of these scavenger cell show various grades of disintegration and finally they disappear (Figs. 149, 150, 151, 152, and 153).

The origin of the corpora amylacea has not been definitely determined. Rene Sand concludes that they are originated from destroyed axis cylinders. Obersteiner and many others believe that they arise from glia cells. Other than the fact of their being found in rows on longitudinal section there is nothing to indicate their origin from the myelin sheath. On the other hand the fact that the corpora amylacea are most numerous where glia nuclei are seen in greatest abundance and that they are most prominent around vessels and septa is suggestive that they arise from glia cells. Around glia cells there is sometimes seen a faint staining hyaline material which is probably the beginning of the amyloid body formation.

DISCUSSION OF THE PATHOGENESIS OF THE LESIONS

It is evident that hemorrhages were not the cause of the degenerations in these cords, for in the many sections examined from various levels hemorrhages were rarely seen and in most of the cords they were entirely absent.

The vascular changes generally were even less than one would expect to find considering the extent of the changes in the other tissues. Our sections definitely confirmed the observations of many neuropathologists that normal, or nearly normal, vessels may be found in sclerotic areas. In other instances when fairly marked vessel changes were present there was usually no definite relation between the vessels and the lesions. To a certain extent the vascular changes may be said to be coördinate with the alterations in the nervous tissue and neuroglia; but even this relationship is not always to be seen.

While noting the frequent lack of sufficient and constant vascular change to explain the cord lesions many observers have believed there was a definite relationship between the vessels and the lesions. As herein stated there have been widely diverging opinions concerning the mechanism of this relationship. Neither has there been an agreement as to the level of the cord best supplied with blood. It has been explained that the gray matter of the cord is exempt from notable involvement because of its better blood supply through the anterior spinal arteries.

Jacob and Moxter, Russell, Batten and Collier, Putnam and Taylor and others regard the anatomic distribution of the peripheral arteries as the deciding factor in the location and symmetry of the lesions. In our sections there was one type of lesion found in apparent relation to the blood vessels or septa. The predominating change was not evidently dependent on the anatomic arrangement of the pial vessels. On the other hand definite changes were found in the gray matter, even before the involvement of the white matter was well marked; furthermore this chromolytic process did not progress coördinately in all the cell groups as apparently should be the case were the changes dependent on vascular relationships.

Largely from the appearance of the Weigert preparations two types of lesions have been described; these are ordinarily termed "recent" and "old" or "areolar" and "sclerotic." Such areas represent respectively early and late stages of the same process. The unstained "sclerotic" or "old" area seen in the Weigert sections differs in its histology according to the degree of advancement of the actual sclerosis; it varies from a mass of glia fibrils with only a few nuclei seen in the sclerotic area. This type of degeneration is probably of toxic origin. The areas involved are not related to any special arterial distribution but do represent the long fibers of the posterior and lateral columns

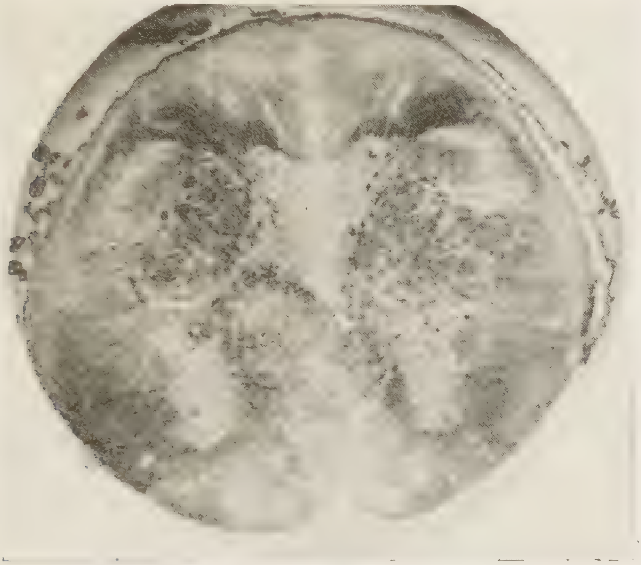


FIG. 154 (Case N 35).—Lower medulla. Ballooned sheaths are numerous in the pyramidal tracts. Old sclerosis in the posterior column and cerebellar tracts. (Weigert.)

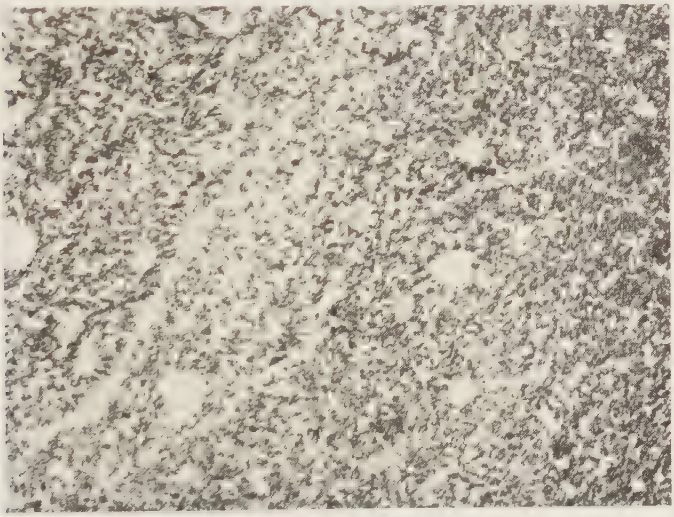


FIG. 155 (Case N 10).—Area in relation to a pial vessel containing no swollen sheaths. Ballooned sheaths are scattered throughout and in groups in the posterior columns. (Weigert.)

and exceptionally the longer fibers of the anterior column. As Putnam, Dejerine, Billings, Hassin and others have suggested the characteristic involvement is a degeneration of the long fibers of the cord and the process is, as Hassin states, essentially a "central neuritis" (Adolph Meyer). Besides the symmetry of the lesions, the location of the areas, and the pathologic changes suggesting a toxic central neuritis, the character of the lesion in the ascending and descending tracts at various levels apparently confirms this view. The degeneration may be of the "areolar" type in one level and the "sclerotic" type in a distant part of the same tract. The more advanced changes are found in the distal portions of the tracts and the recent changes, the ballooning of the sheaths and involvement of the neurofibrils, are found nearer the cells from which the axons arise. Therefore in the upper cervical levels we find old sclerosis in the central parts of the posterior column with less advanced changes in the column of Burdach; likewise in the cerebellar tracts the changes are more advanced in the upper cord (Figs 154 and 155). In the descending tracts the older lesions are in the lower levels of the cord with more ballooned sheaths seen in the upper regions. In other words, as has been pointed out, the parts of the neurons farthest removed from their trophic center are primarily involved. The descriptive term given to this disease by Dejerine, "*le syndrome des fibers radiculaires longes dues cordons posterieurs*" is apt.

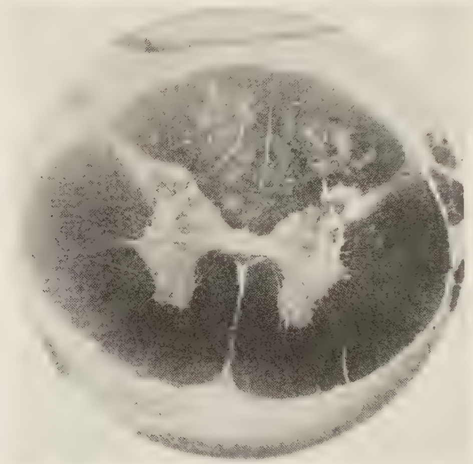


Fig. 156 (Case N 10).—First lumbar segment of the spinal cord. Several areas with vessels in center, also groups of, and individual, ballooned sheaths not in relation to vessels. (Weigert.)

Besides the foregoing type of lesion another change is found fairly frequently, although much less characteristic than the degeneration of the long fibers of the cord involvement, in pernicious anemia. Areas of this type are in definite relation to blood vessels and appear in the Weigert sections as "sclerotic" areas surrounding a blood vessel or septum and containing a greater or lesser number of normal or atrophic sheaths. Ballooned sheaths are practically never a part of this picture, and finding them in relation to such an area is probably a coincidence (Fig. 156). The vessels in these areas may have marked thickening of the adventitia but not infrequently they appear fairly normal. In the general stains the "sclerosis" is seen to consist of a hyalin-like supstance, although in some areas a number of granule cells are seen, esepcially surrounding the vessel. These areas vary from segment to segment although it seems likely that a certain amount of secondary degeneration occurs as a result of the perivascular lesions.

CONCLUSIONS

1. Two types of lesions predominate in the cord involvement commonly associated with primary anemia.

2. The lesion more characteristic of the changes in these cords consists of a degeneration of the long fibers of the cord, particularly of those in the posterior column. This type of lesion does not depend on the arterial distribution.

3. A less distinctive process is a perivascular area having normal or atrophic sheaths scattered through the area. These discrete areas vary in different levels of the cord.

4. Changes in the cells of the anterior horn and Clarke's column are often of early occurrence but are probably not the primary factor in the degenerative changes in the white matter since the involvement of the fibers occurs without marked changes in the gray matter. However, it is likely that the cell changes do play a part in the rapidity of the changes of the lesions and possibly also in the character.

5. Hemorrhages, thrombosis, and adventitial thickening are found, but are not constant or frequent enough to account for the degeneration.

6. The changes in the spinal cord are strongly suggestive of a toxic etiology.

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EXPERIMENTAL AND CLINICAL RESULTS OF NERVE ANASTOMOSIS*

ALFRED W. ADSON

In reviewing the literature on nerve anastomosis, the modern work may be said to have been begun by von Büngar in 1891, by Howell and Huber, in 1892, by Ströbe, in 1890, and by Huber, in 1895. von Büngar called attention to the nucleated protoplasmic bands which have occupied a prominent place in the histogenesis of regenerated nerve fibers. He emphasized the point that the nuclei of the neurolemma increase in number and that the protoplasm accumulates about them. Howell and Huber observed the presence of protoplasmic bands (Bandfäsern), but regarded them as embryonic nerve fibers capable of receiving and transmitting impulses. Ströbe was able to demonstrate the outgrowth of axons from the central end but believed that the myeline sheath was formed as a continuation of the old sheath. Huber, working with Ströbe's technic, was able to show that the axons grow from the central stump and in some cases enter the substance of protoplasmic bands in the distal segment. Two theories of regeneration were held at this time, the first, presented by Waller, in 1852, that the axons grow out from the central end, and that complete degeneration takes place from the severance of the nerve proximal to the node of Ranvier and distally through the entire peripheral nerve; the second, that the axons do not degenerate in the peripheral stump after they have been separated and that all that is necessary for an axon to functionate is the fusion with the central axon and the development of the new myeline sheath around it. Further investigative work, particularly that of Ranson in 1912, has proved the former theory, that is, that degeneration is followed by regeneration.

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* Abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery, 1918.

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During the development of nerve anastomoses numerous methods have been employed. Lètièvant suggested making flaps from either the central stump or the peripheral stump of the divided nerve, or from both the central and peripheral stumps. When it has been impossible to bring about an immediate approximation of the nerve ends, various materials have been used to bridge the gap. Assaky recommended a bridge of catgut between the severed end; Vanlair, decalcified bone tubes; Payr, magnesium tubes; Forssman, celluloid tubes; Lotheissen, gelatin tubes; Foramitti, hardened arteries of the calf, Denk, Döffner, Kredel, and Lewis and Kirk, fascia lata tubulization; Corbett and Beckman, vein tubulization; Sherren, Cargile membranes; Auerbach, galalith; Assaky and Huber, nerve transplants, and Feiss, the fusion method of overlapping the ends and ligating them with silk or chromic catgut.

Many of these methods have been discarded; the ones most commonly employed are (1) the flap method, (2) the fusion method, (3) fascial tubulization, (4) vein tubulization, (5) Cargile membranes, and (6) nerve transplants.

It was the author's hope to try out the different methods in order to compare end results. The experimental study was carried over a period of two and one-half years, during which time seventy-six dogs were operated on and 189 operations performed. Twenty-four of the seventy-six dogs either died too soon to show results, or the specimens obtained were destroyed in preparation, leaving fifty-two dogs, with 112 operations, in which valuable results were obtained. These operations form the basis of the report.

The nerves used during the experimental study were the posterior tibials, the femorals, the sciatics, the external popliteals and internal popliteals, and the ulnars. It was found that the small nerves such as the femorals and posterior tibials were not so satisfactory as the ulnars and sciatics. The ulnars were preferable to the sciatics inasmuch as an operation on the former did not so greatly incapacitate the dog. The following types of operation were performed:

Plastic (nerve flap split and turned)	4
Fusion (nerve overlapped and ligated with silk)	15
Fusion (nerve overlapped and ligated with catgut)	6
Nerves cut and permitted to fall into sheath	13
Anastomosis with silk with fascial covering	10
Fascial tubulization (Lewis and Kirk)	6
Vein tubulization (Corbett)	6
Anastomosis with silk and animal membrane covering	18
Anastomosis with silk and vein covering (Beckman)	6
Anastomosis with chromic catgut	2
Anastomosis with silk without covering	7
Anastomosis with silk with bone-tube covering	3
Anastomosis with silk with fiber-tube covering	1
Autogenous transplants	3
Nerves crushed with forceps	5
Nerves ligated with catgut	4
Nerves ligated with silk	3

The average duration of anastomosis was five months; the distance between the anastomosed ends varied from 1.2 mm. to 15 mm. The degree of regeneration was determined by (1) the physiologic result, (2) the electric reaction, and (3) the histologic result. The electric reactions were tested at the time the dogs were sacrificed, and the end was stimulated below the point of anastomosis by the Harvard induction coil.

A general summary of the experimental results shows that of the 112 dogs operated on, 105 gave signs of regeneration; seven operations were complete failures. The approximate degree of regeneration from an anatomic point of view was 64 per cent, from electric reaction about 63 per cent, and from an histologic standpoint 75 per cent. Each record was made independently of the others; similar readings for each test are evidence that regeneration does not occur completely.

Further study of forty-one patients operated on for nerve injury was made; nerves as follows were operated on: facial nine cases, ulnar seven cases, radial one case, median seven cases, musculospiral ten cases, external popliteal four cases, sciatic two cases, and right recurrent laryngeal one case. The average duration of injury before repair was twelve months. The types of operation employed varied from simple end-to-end anastomosis with catgut to plastic-flap operations; other types were anastomosis with silk, with fascial covering, with vein covering, and without covering. In summarizing it may be said that 19.5 per cent of the patients had plastic flap operations, 80.5 per cent end-to-end anastomosis; 27 per cent had interneural gaps, varying from 2.5 cm. to 6.87 cm., and 73 per cent had no gap, or no record of a gap in their histories. The results in 10 per cent of the patients were indeterminate, 73 per cent of the patients were improved, and the operations in 17 per cent were complete failures.

The study of the experimental and clinical results reveals that the ideal nerve anastomosis was end-to-end with fine interrupted silk sutures in the sheath. Fascial membrane, vein covering, and tubes were of no particular value. The interposition of autogenous and heterotogenous grafts permitted regeneration, provided the distance between the nerve ends was not too great. Perhaps in animal experiments it has increased the percentage of regeneration, but clinically in patients it has not. The author believes that the degree of regeneration depends on the duration of the injury previous to operation, the shorter the interval the better the results (failure after three years); on the removal of neuromas; and on apposition of nerve ends. If the distance is not more than 1 cm. slight recovery can be expected, but if it is greater very little can be hoped for, since scar tissue develops before the axons reach the distal segment.

NEUROBLASTOMA SYMPATHICUM: REPORT OF ONE CASE*

PAUL C. GUNBY

The case reported is that of a boy, aged 13, who came to the Mayo Clinic complaining of weakness, failing vision, and scalp nodules. Another child in the family had "skull necrosis," and the mother gave a history of four miscarriages. Pallor, loss of strength, and failing vision were of six months' duration, and had progressed since onset. Pain in the hips and knees had appeared early.

Clinical examination revealed moderate emaciation, pale, greenish skin, and a nodular condition of the entire vertex and forehead. These nodules varied from hard to soft in consistency and apparently were attached to the cranial bones. The superficial veins of the scalp were dilated. Bilateral exophthalmos was present in moderate degree. Hard bilateral cervical glands were palpable; pressure over the sternum and ribs elicited extreme tenderness. In the right hypochondrium a smooth liver edge was palpable; on the left a smooth mass was felt which suggested the spleen.

The eye grounds revealed bilateral choked disc of two diopters; hemoglobin (Dare) was 30 per cent, erythrocytes 1,580,000, leukocytes 6,200. The differential blood count was normal and the blood-Wassermann reaction was negative on the patient and the father.

In a roentgenogram of the skull, metastasis was suggested by the diffuse porosity.

A diagnosis of neuroblastoma sympathicum was suggested, but anti-luetic therapy was instituted because of the suspicious family history. Death from terminal bronchopneumonia occurred in two months.

Postmortem examination disclosed a large tumor of the left adrenal gland with metastasis to bones of the skull (Figs. 157 and 158), sternum, vertebrae, ribs, and retroperitoneal lymp glands.

Histologic examination confirmed the diagnosis. Rosette formations (Fig. 159) and primitive sympathetic ganglia (Fig. 160) were present.

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* Abstract of paper published in full in the American Journal of Medical Sciences, 1920, clx, 207–214. Copyright, Lea and Febiger, Philadelphia.

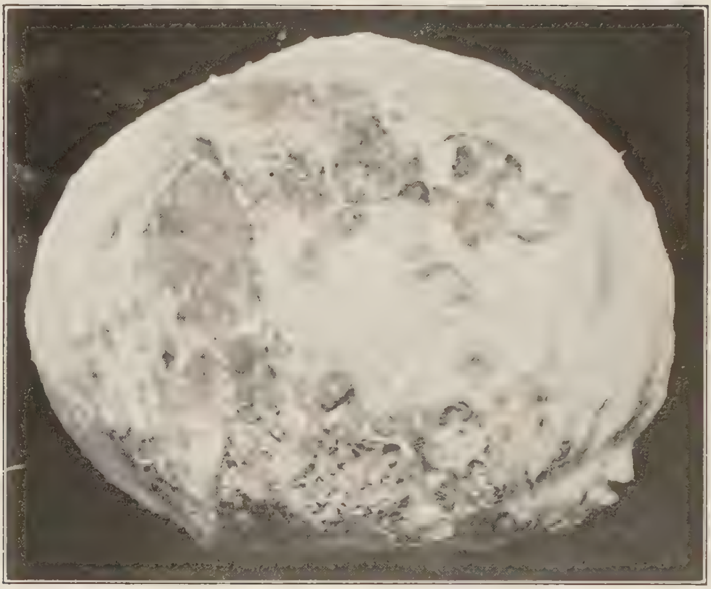

Fig. 157.—Outer surface of the calvarium.

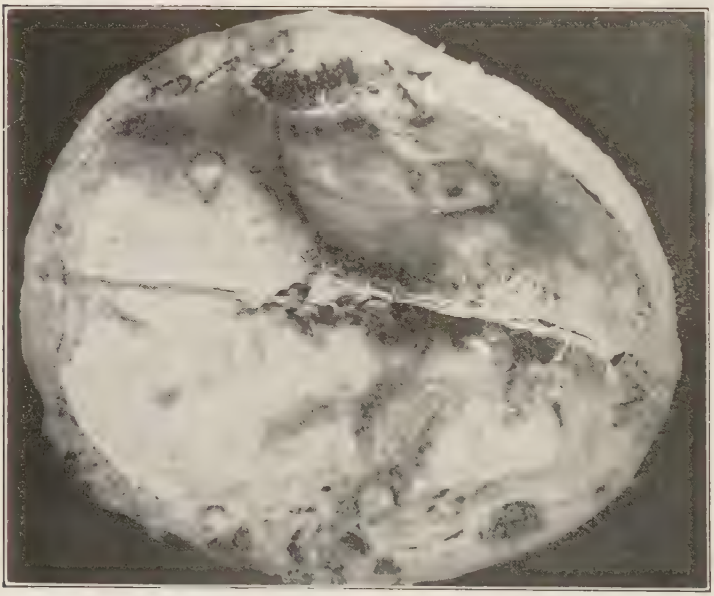

Fig. 158.—Inner surface of the calvarium.

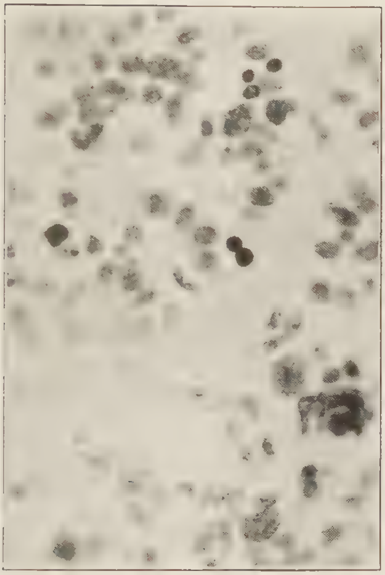

Fig. 159.—Great variation in the size and form of tumor cells; rosette in the center of the field. ×500.

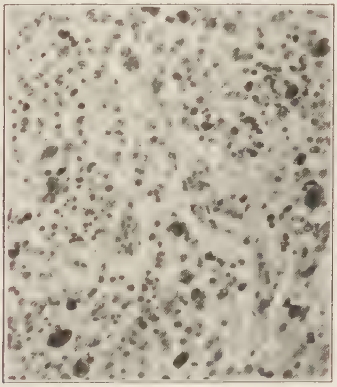

Fig. 160.—Two primitive ganglia in the field. Many tumor giant cells with one foreign-body giant cell near the top of the field.

THE INFLUENCE OF THE VAGUS NERVES ON RESPIRATION*

CHARLES C. GAULT

The factors which produce an effect on respiration may be classed under two heads: factors that produce their effect through a chemical alteration of the blood, and factors that produce their effect through impulses conducted by the extrinsic nerves. The effect of these various factors on respiration is directly concerned with the alterations which they produce in the respiratory center. Whether they bear directly on a single respiratory center located in the medulla or on a number of such centers, as has been suggested by Brown-Sequard, the fact remains that the respiratory rhythm in an animal in which the extrinsic influences have been destroyed as far as possible is notably different from that of normal respiration.

Previous investigations have shown that alterations in the chemical composition of the blood supplying the respiratory center serve as one of the chief regulating factors of respiration. Of the chemical factors the gaseous composition of the blood plays the most important part. That this should be so is at once apparent from the fact that the primary function of respiration is to supply the living organism with oxygen and to remove the gaseous products of metabolism, especially carbon dioxid. Changes of very small extent in the carbon dioxid tension of the blood produce profound alterations in the rate and depth of respiration in the normal animal, an increase of carbon dioxid tension initiating an increased respiratory action whereby the gaseous content of the blood is brought back to normal. The response of the respiratory center to a decrease of oxygen tension is not so delicate, and rather wide changes may occur in the oxygen content of the inspired air before a marked alteration in the respiratory movements is produced. From the work of previous investigators the decrease of oxygen tension has been shown to play little if any part in the normal regulation of respiration. The lack of oxygen is still believed by some (Verworn) to be one of the important regulating factors in normal respiration.

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* Abridgment of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Arts, 1917.

Speck has advanced the theory that the hyperpnea induced in the organism by increased amounts of carbon dioxid is not due to a direct action on the respiratory center but to a sensory stimulation of the nerve endings of the pulmonary vagus fibers from a local dyspnea. Later work by Haldane and Smith, which has since been corroborated by Boothby and Shamoff, has shown that stimulation of the vagus nerve endings by carbon dioxid has nothing to do with hyperpnea.

The effect of the vagus nerves on respiration has long been a subject of investigation. Traube showed that by stimulation of the vagus nerves respiration is arrested in the inspiratory phase. These experiments have since been performed by numerous investigators with varying results, depending on the degree and strength of stimulation.

Demonstration of the influence of the vagus nerves on the respiratory center has been attempted also by section of the nerves. Lewandowsky and others have noted a prolongation of the inspiratory phase after cutting the vagi. The objection raised to this procedure has been that the effect observed may not be due alone to section of the pulmonary fibers but rather to a disturbance of the general metabolism of the body by blocking the impulses which would be conducted to other parts of the body. However, since the response of the respiratory mechanism to section of the vagus nerves is instantaneous it is difficult to imagine that the alterations are caused indirectly by a disturbance of the metabolic processes. Other investigators have advanced the objection that the first response of the respiratory musculature to section of the vagi is the result of reflex stimulation due to cutting. That such a stimulation occasionally occurs is easily demonstrable, but in these cases the response is not a prolonged inspiratory phase, but rather a hyperpnea which soon passes over to the typical vagus breathing with increased depth and prolonged inspiration.

Stewart and Pike have shown that in animals that survive after section of the vagus nerves for a considerable length of time the heart beat which is at first much increased in rate returns to normal after a number of days. The respiratory rate, however, remains persistently much slower and markedly prolonged in the inspiratory phase. In such animals the rate of respiration is not affected to so great a degree by psychic stimuli as normally.

Boothby and Shamoff have shown that in dogs in which the intrathoracic pulmonary fibers of the vagus nerves are sectioned the respiration is unaltered after a number of months. They conclude therefore, that the pulmonary branches of the vagus nerves do not possess any demonstrable power over the normal regulation of the gaseous metabolism, the pulmonary ventilation, or the gaseous exchange in the lungs. The fact that the results of these investigators failed to demonstrate any vital function of the pulmonary vagus fibers may be owing to two causes. The pulmonary fibers from the vagus are given off in the thorax and are closely intermingled with the pulmonary nerve plexuses at the roots of the lungs so that section of the pulmonary fibers in the thorax is very difficult and may, in a number of cases, be incomplete. In cases in which all of the pulmonary fibers are not sectioned, the vagus control will still be present. Section of one vagus trunk in the cervical region, the other being intact, except in a few cases will produce no effect on the nature of the respiratory movements. In the cases in which section of one cervical vagus produces a typical vagus breathing, section of the second vagus is without effect. The regulating influence of the vagus on the respiratory center is, therefore, able to manifest itself when many of the pulmonary vagus fibers are destroyed. Again, the results obtained by Boothby and Shamoff by section of the intrathoracic vagus fibers may be explained by general differences in the physiologic response of the various laboratory animals to different stimuli. It was with the desire to determine what differences, if any, exist in the function of the pulmonary vagus fibers in the various animals that this series of investigations was undertaken.

EXPERIMENTAL

The investigations were performed on rabbits, cats, and dogs. Anesthesia was produced by chloral hydrate and ether in rabbits, by chloroform followed by ethyl urethane and small amounts of ether in cats, and by morphin sulfate and ether in dogs. The respiratory movements were recorded by two methods. In the first experiments a T-shaped cannula was inserted into the cervical portion of the trachea. One part of the cannula was left open to the air so that during most of the experiment the animal breathed air containing normal amounts of oxygen and carbon dioxid. The other part of the cannula was connected with a large bottle containing in the bottom concentrated sodium hydroxid solution, which in turn was connected with an aluminum spirometer of small size and weight, the movements of which were recorded directly on the kymograph. This method prevented an excess of carbon dioxid in the air respired and the bottle was large enough so that the oxygen content of the air was not materially decreased.

In the later experiments the respiration was recorded by means of a lever inserted through a small opening in the middle line of the anterior abdominal wall so that it rested against the diaphragm. This latter arrangement was considered the more accurate, and the lever often recorded the heart beat also. The free end of the lever was attached by a silk thread to a second lever which recorded the movements of the diaphragm on the kymograph.

The elimination of the effect of the vagus nerves on the respiratory center was accomplished by two methods.

First method.—The vagi were exposed in the neck and placed on U-shaped hollow glass thermodes, which were in turn attached to a reservoir containing ice and brine. The vagi were then cooled to from 0° to −0.5°C. by allowing the brine to run through the thermodes. In this way the impulses passing over the vagus nerves were blocked and the effect on respiration of the elimination of vagus regulation could be observed. By allowing warm water of about 30° to 35°C. to pass through the thermodes the vagus block was destroyed and the respiration returned to normal. After the vagi had again become functional they were sectioned and the effect of the destruction of the vagus influence was again observed. The effect of physiologic section of the vagi with cold in all cases showed the same effects as that of anatomic section of the nerves.

Figures 161 and 162 show the similarity in the response of rabbits, cats, and dogs to vagus block, whether produced by cooling or section of the nerves. We find, as have many investigators, that the response to a vagus block is seen in a slower and deeper respiration with a markedly lengthened inspiratory phase. In most cases section of one nerve produced no effect either on the respiratory phases or on the rhythm, beyond the production of an irregular increase in rate of short duration due to stimulation of the nerve by cutting (Fig. 163). A similar stimulation was occasionally produced by cooling the nerves. This effect diappeared after three or four respiratory cycles.

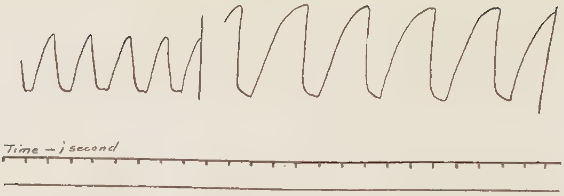

FIG. 161.—Comparison of respiration in the cat before and after section of the vagi. Tracing made by the spirometer method. Upstroke, inspiration.

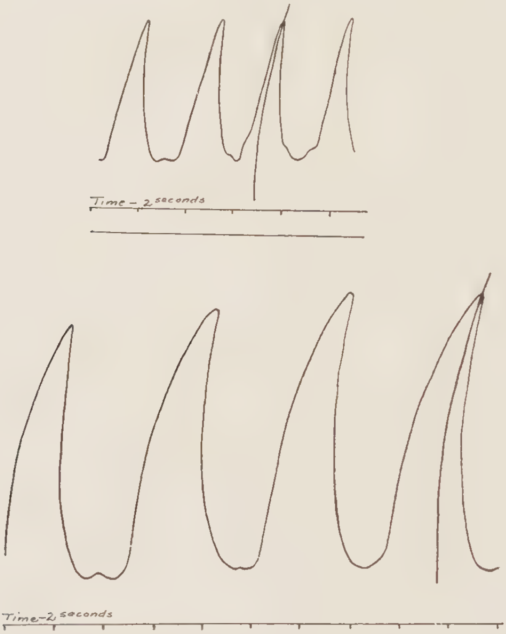

FIG. 162.—Dog. Comparison of respiration before and after section of the vagi. The upper tracing represents the normal respiration. Tracing made by spirometer method. Upstroke, inspiration.

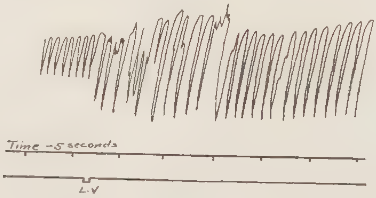

FIG. 163.—Rabbit. Mechanical stimulation by section of the left vagus (L.V.). Previous section of the right vagus was without effect. Tracing made by the spirometer method. Upstroke, inspiration.

Second method.—In a few cases section of one vagus nerve, the other being intact, produced an effect on respiration. When this effect was quite marked section of the other vagus was without effect.

Tables 1, 2 and 3 show the effects of section of the vagus nerves on the respiratory ratio, the rate, and depth of the respiration. A study of these tables shows that in all the animals studied the effect of blocking the vagus impulses, whether by means of cooling or by anatomic section, is essentially the same.

Table 1.—The Effect of Section and Cooling of Both Vagus Nerves on the Respiratory Ratio*

	Date	Normal	Vagi cooled	Vagi warmed	Vagi cut
Rabbit.........	10-23-16	1:1.4	1:0.8	1:1.3	1:0.88
Rabbit.........	10-27-16	1:1.01	1:0.83	1:1.1	1:0.9
Cat............	11- 3-16	1:1.4	1:0.66	1:1.5	1:0.65
Cat............	11- 6-16	1:0.75	1:0.6	1:0.76	1:0.7
Cat............	11-10-16	1:0.75	1:0.5	1:0.74	1:0.45
Dog..	11-17-16	1:2.2	1:2		1:0.83
Cat............	11-24-16	1:1.1	1:0.83	1:1.3	1:0.63
Cat..	3-2-17	1:1.1	2:1.1		
Cat...	3-9-17	1:1.17	1:0.7		
Cat............	3-24-17	1:1.2	1:0.82		
Cat............	3-30-17	1:1.1	1:1		
Cat............	3-31-17	1:1.1	1:0.56		
Rabbit.........	4- 6-17	1:1.3	1:0.89	1:1.5	1:0.87
Dog............	4-16-17	1:1.9	1:1.1		1:0.8

*The ratio of the duration of the inspiratory phase to the expiratory phase.

Table 2.—The Effect of Section and Cooling of Both Vagus Nerves on the Respiratory Rate

	Date	Normal	Vagi cooled	Vagi warmed	Vagi cut
Rabbit.........	10-23-16	55	33	49	36
Rabbit.........	10-27-16	49	35	49	36
Cat............	11- 3-16	30	12	30	18
Cat............	11- 6-16	28	18	28	19
Cat............	11-10-16	28	13	27	10
Dog............	11-17-16	25	11		11
Cat............	11-24-16	13	9	13	6
Cat............	3- 2-17	30	13		15
Cat............	3- 9-17	36	21		
Cat............	3-24-17	66	36		
Cat............	3-30-17	25	14		
Cat............	3-31-17	28	13		
Rabbit.........	4- 6-17	72	40	51	43
Dog............	4-16-17	30	19		19

TABLE 3.—THE EFFECT OF COOLING OR SECTION OF BOTH VAGUS NERVES ON THE DEPTH RESPIRATION REPRESENTED BY THE HEIGHT OF THE EXCURSIONS ON THE KYMOGRAPH

	Date	Normal, mm.	Vagi cooled, mm.	Vagi warmed, mm.	Vagi cut, mm.
Rabbit	10–23–16	8.5	15.2		15.0 S
Rabbit	10–27–16	7.5	12.0	8.1	15.4 S
Cat.	11– 3–16	11.0	22.0		15.0 S
Cat.	11– 6–16	14.0	30.0		26.0 S
Cat.	11–10–16	15.0	22.0		18.0 S
Dog.	11–17–16	40.0	75.0		75.0 S
Cat.	11–24–16	17.0	37.0		59.0 S
Cat.	3– 2–17	46.0	54.0		54.0
Cat.	3– 9–17	26.0	31.0		
Cat.	3–23–17	25.0	35.0		
Cat.	3–24–17	31.0	45.0		
Cat.	3–30–17	38.0	58.0		
Cat.	3–31–17	20.0	31.0		
Rabbit.	4– 6–17	16.0	20.0		
Dog.	4–16–17	35.0	70.0		

In Table 3, the figures corresponding to the animals marked *S* were obtained from tracings made by means of the spirometer method described. These may be read in terms of cubic centimeters by using 100 c. c. as an equivalent of 50 mm. The other figures were obtained from tracings made by means of the lever inserted below the diaphragm and are not so easily transposed.

While the tabulated results show essentially the same effects of vagus block, in certain respects the various animals respond quite differently. The main difference observed in the rabbit, cat, and dog in the response to section of the vagi is the varying degree of regularity of the respiratory movements after the influence of the vagus nerves on the respiratory center has been destroyed. In all of these animals the respiration is slower and deeper and shows an increased inspiratory phase.

The respiration following section of the vagi in the rabbit is markedly regular and except for the classical symptoms of destruction of the vagus influence no changes are observed in the respiratory cycles. In the cat the respiration which is normally regular in depth and time of the respiratory cycles is changed to one in which various irregularities appear at widely differing intervals (Fig. 164). These

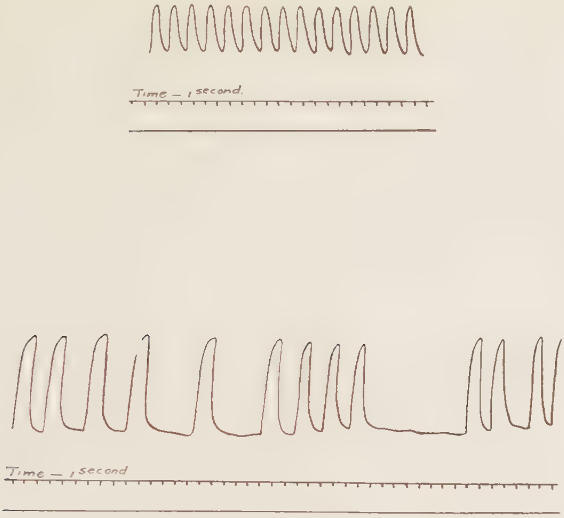

Fig. 164.—Cat. Tracings showing the production of irregularities in the respiratory rhythm following vagus section. Upper tracing is normal respiration. Tracings made by spirometer method. Downstroke, inspiration.

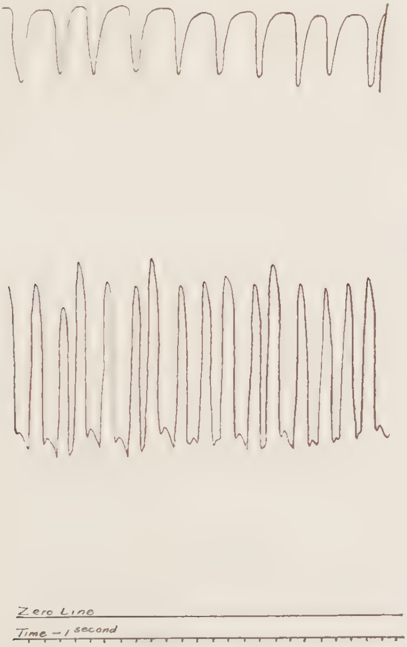

Fig. 165.—Dog. Tracings of normal respiration and normal carotid blood pressure. For comparison with Figure 166. Respiratory tracings made by lever method previously described. Downstroke, inspiration.

irregularities which appear in the cat after section of the vagi are much more pronounced in the dog (Figs. 165 and 166), and only occasionally are two consecutive respiratory cycles completed in which the depth and time of the respiratory movements are equal.

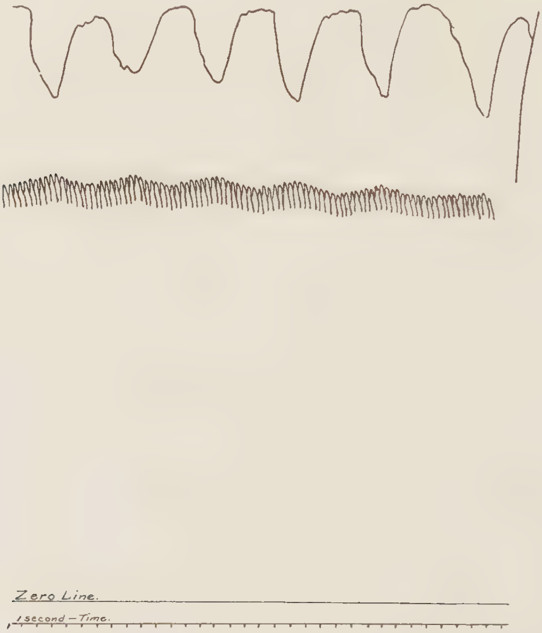

FIG. 166.—Dog. Tracing showing ataxic type of respiration produced by section of both vagus nerves. Upper tracing, respiration. Lower tracing, blood pressure. Same method as Figure 165.

THE RESPONSE OF THE RESPIRATORY CENTER TO CHANGES IN COMPOSITION OF THE INSPIRED AIR

The experiments in this investigation, performed to determine the effect of changes in the inspired air, show, as has the work of previous investigators, that the normal animal accommodates itself to an excess of carbon dioxid by an increased rate and depth of respiration.

Bernstein, using inspired air containing from 10 per cent to 25 per cent carbon dioxid has shown that the normal animal responds by an increased rate and depth of respiration, but that after section of the vagi the respiratory rhythm is always decreased.

Gad and Rosenthal find that section of the vagus nerves produces no effect in the response of the animal to an excess of carbon dioxid.

In either case increased carbon dioxid content produces an increased rhythm.

Plavec, in his work on the effect of changes in the blood gases on respiration, found that normally the animal responded with an increased rate of respiration to an excess of carbon dioxid in the inspired air, provided the amount of carbon dioxid was not above 10 per cent. With higher percentages there was a slight diminution in the frequency. He found also that after division of the vagi the frequency is not altered to an appreciable extent.

Hill and Flack have obtained a decreased respiratory rhythm by causing the animal, after section of the vagi, to breathe an excess of carbon dioxid. The amounts of carbon dioxid used in these investigations were quite large, and the results obtained may be compared with those produced by asphyxia.

Scott has shown that after section of the vagi in rabbits an excess of carbon dioxid results in an increased depth of respiration. The rate, however, which in normal animals is greatly increased, is practically unaltered after section of these nerves. A similar result has been obtained by greatly diminishing the oxygen content of the inspired air. He has shown moreover that animals with divided vagi are capable of accommodating themselves quite well to changes in the inspired air, provided the changes are not too great. If the change in the gaseous composition exceeds a certain point, however, the accommodative mechanism breaks down.

Boothby and Shamoff found no essential difference in the response to changes in the gaseous composition of the inspired air in dogs in which only the intrathoracic pulmonary branches of the vagus nerves were sectioned. Their curves show an increase in frequency and were sectioned. Their curves show an increase in frequency and depth of breathing as a result of an excess of carbon dioxid (0.51 per cent to 6.03 per cent). With a decrease of the oxygen of the inspired air the respirations increased quite markedly in frequency but only slightly in depth. They conclude, therefore, that "the vagus nerve does not contain fibers which transmit impulses arising from variations in the composition of the alveolar air."

In the experiments recorded in this paper the air containing an excess of carbon dioxid was put in parchment bags, which were connected to the tracheal cannula so that the animal breathed directly from the bag. Very small amounts of carbon dioxid were used so that any effects obtained would not be due to asphyxia.

We find that the three principal laboratory animals (rabbits, cats, and dogs) respond in essentially the same manner to an excess of carbon dioxid both before and after section of the vagi. The response of the normal animal is seen in a marked increase in frequency and depth of respiration (Fig. 167).

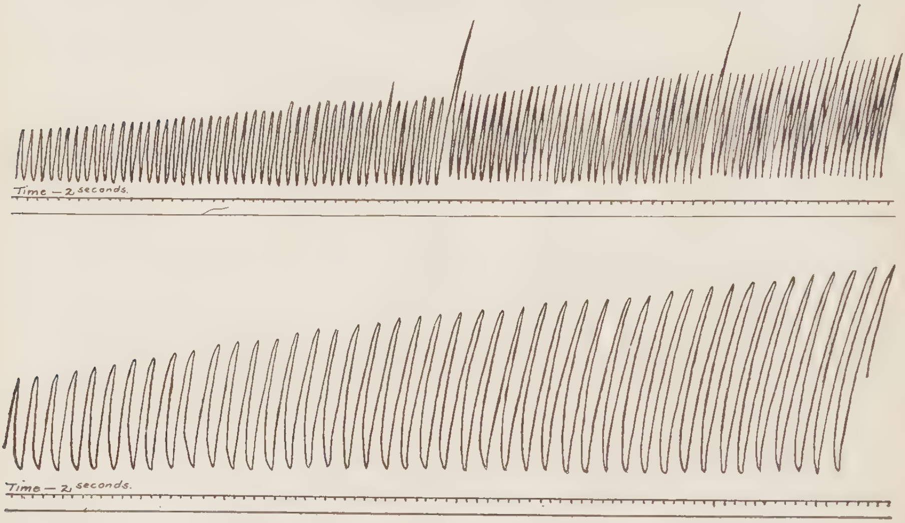

Fig. 167.—Cat. Effect of increased amounts of carbon dioxid on respiration. Upper tracing, normal. Lower tracing, after section of the vagi. Spirometer method. Upstroke, inspiration.

The results obtained in my experiments on the effect of an excess of carbon dioxid on animals in which the vagi were sectioned agree with the results obtained by Scott in his experiments with rabbits. After section of the vagi the animal responds with an increased depth of respiration. The frequency, however, is practically unaltered. The curves showing the effect of vagus section on the response to carbon dioxid in the inspired air were made from the same animal and with the same mixture of gas. In this way the differences observed could be attributed only to section of the nerves, and not to sources of experimental error.

Both normal animals and animals in which the vagi have been sectioned respond to an excess of carbon dioxid by an increase in the depth of respiration. Normal animals alone respond by an increase in the frequency of respiration. From the results obtained in these experiments we may conclude that the increased tidal volume due to an excess of carbon dioxid is in no way dependent on the influence of the vagus impulses on the respiratory center, but that this phase of the response of the normal animal is dependent solely on the tension of the carbon dioxid in the blood stream. The control of the other phase in the response of the animal in which the vagi are intact, that is, the increase in frequency, must be attributed to the influence of the vagus impulses on the respiratory center.

THEORETICAL

In a consideration of the specific function of the vagus nerves in the regulation of the respiratory movements, a consideration of some of the more important theories which have been previously advanced will not be out of place.

It was first shown by Hering and Breuer that expansion of the lungs produces an inhibitory influence on inspiration. These investigators have also stated that collapse of the lungs tends to produce an inspiratory effort. In the light of these facts they formulated a theory which attributed the normal respiratory rhythm to a self-regulation on the part of the respiratory mechanism. This regulation they believed to occur through two sets of fibers in the vagus nerves, one set being stimulated by expansion of the lungs in inspiration tending to produce an expiration. At the end of expiration the second set of fibers is stimulated by the collapse of the lungs, causing an inspiratory effect. This theory, however, has not been universally accepted, for, while the fundamental facts have not been disputed, it is not clear to everyone that collapse of the lungs at the end of expiration forms a specific stimulus to inspiration.

Gad has accepted this reflex theory for the inhibition of inspiration only. As the cause for inspiration, Gad argues for a constant inspiratory stimulus which resides in the respiratory center. This inspiratory impulse originates, therefore, automatically or resides in the respiratory center and is interrupted only by the expiratory impulse produced by the expansion of the lungs.

Meltzer, in advancing a theory to explain the function of the vagi in respiration, has advanced a modification of the original theory of Hering and Breuer. He assumes that the vagus nerve contains two sets of pulmonary fibers, those producing inspiration and those inhibiting inspiration. These fibers participate equally in the production of the respiratory rhythm. He does not, however, accept the statement of Hering and Breuer that the fibers producing inspiration are stimulated by the collapse of the lungs at the end of expiration. Rather he assumes that the action of these two sets of pulmonary fibers is similar to the action of the vagus and accelerator nerves on the heart. Conjoint stimulation of the vagus and accelerator nerves causes at first a slowing or stopping of the heart followed by an increased rhythm after stimulation. Of the two sets of cardiac fibers the vagus fibers produce an immediate effect, while the influence of the stimulation of the accelerator fibers is seen in a long after-effect. Meltzer ascribes a similar state of affairs to the regulation of respiration. Both the inspiratory and expiratory pulmonary fibers are stimulated by the expansion of the lungs at the end of inspiration. The stimulation of the expiratory fibers, in a way analogous to the effect of stimulation of the cardiac vagus fibers, produces an immediate effect, while the inspiratory fibers manifest themselves in a prolonged after-effect following stimulation, and induce an inspiratory action at the end of expiration. Of the numerous theories advanced in an attempt to explain the function of the vagi in the regulation of respiration, no single theory may be said to have been universally accepted.

Scott has drawn a striking comparison between the action of the vagus nerves in respiration and the action of the sensory nerves in the control of other movements of voluntary muscles. Such an explanation brings the action of the vagus nerves into accord with the general physiologic law that any properly regulated movement not only involves the use of motor nerves but also a sensory supply, the function of which is to control and modify the action of the muscles concerned in the movement so that a regular and orderly movement may be produced. When the sensory supply to a part of the body is destroyed, the movements of that part become ataxic. In a similar way Scott argues that destruction of the vagus influence results in an ataxic respiration.

My experimental work showed that after section of the vagus nerves the regularity of the respiratory rhythm is interrupted, and that the movements are, therefore, more or less ataxic. The cause for these irregularities may be ascribed to two factors: first, loss of sensory control over the acting muscles, and second, influences brought to bear on the respiratory center by other factors. Since the respiratory center is essentially automatic, it is to be expected that impulses from the center will be sent out in orderly succession so long as the center is not affected by extrinsic impulses of any sort. After the principal sensory nerve supply through the vagus nerves has been destroyed it is possible that other variable factors, for example, very minute changes in the gaseous composition of the blood, and so forth are able to influence the rhythmic discharge from the respiratory center with greater facility. The fact that in the normal animal these varying irregularities do not appear, or at least appear less frequently, is in accord with the theory that the vagus acts to a great degree as a stabilizer for the respiratory center, and causes the respiratory movements, which would otherwise become ataxic, to be accurately coördinated.

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THE GRAPHIC RECORDING OF REFLEXES, CLONUS, AND TREMORS*

R. EDWIN MORRIS

In undertaking this work, two great problems were confronted; the securing of consistent constant graphic records of the reflexes, clonus, and tremors and their interpretation and the underlying physiologic basis.

A new field has been opened in the study of nervous phenomena, so that a more definite study of the various functions of the brain, cord, and its terminals may be made. The reflexes themselves have been widely studied and much has been written thereon. The knee jerk, the most accessible for study, has offered a fruitful field of investigation. To the clinician the knee jerk appears increased, diminished or absent.

The writer has devised several new appliances, among them a device for recording the mechanical swing of the leg simultaneously and on the same moving photographic paper with the record of the electric action of the string galvanometer (Cambridge modification of the Einthoven string galvanometer, or electrocardiograph).

Attention has been centered on the study of the knee jerk and in recording this reflex. The apparatus employed consists of a chair with arms and back, in order that the patient may sit in as comfortable a position as possible. The chair is elevated sufficiently so that the feet swing free from the floor. Attached to the front edge of the chair are two light boards that are fastened to the back of the patient's leg. The upper end of each board is attached by a hinged joint to a rod that runs along the front edge of the chair, permitting a lateral movement in order to adjust the leg boards comfortably to the legs of the patient. A vertical rod passes through the center of the front edge of the chair passing through a collar and is held in place by a set screw so that it can be raised or lowered in adjusting the hammer position. The rod bends forward at right angles at the upper end and to this is attached a double set screw which holds in position a rod that passes at right angles to the forward end of the hammer support and is parallel to the front edge of the chair. This rod supports the hammer in position so that with proper adjustment it will strike the knee in the same spot each time and give blows of the same intensity as many times as desired.

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In securing records, the subject is seated in the chair, attachments are made to the galvanometer by means of electrodes similar to those used in electrocardiographic work, one electrode being placed on the knee and one on the chair so that it comes in contact with the sacral region. The apparatus for securing the mechanical swing consists of the swing board in the inner edge of which are inserted three eyelets, to one of which is attached a hook which is secured to an inelastic cord which runs over an adjustable frictionless pulley to a hanging indicator suspended in front of the aperture in front of the lens of the electrocardiograph. The indicator produces a shadow parallel to that of the string galvanometer. Holding the indicator in position on the other side is a coiled steel spring, the tension of which is adjustable. So long as the indicator remains in a vertical position the tension on the string leading to the swing board is constant. This apparatus has given very constant and satisfactory results and produces a record that is of the highest value.

The record, as it appears, from a comparative point of view at the extreme left or upper side of the paper as ordinarily held, indicates the movement of the time marker: next comes the record of the galvanometer string: and then the record of the mechanical indicator: and at the extreme right or lower side of the record is the record of the time indicator.

As a routine practise in recording knee jerks, three records of each limb are made, starting with the left: first the knee jerk, then the knee jerk doubly reinforced, and then a voluntary swing representing as nearly as possible the swing produced by the reflex.

The initial reflex action is evidenced by the rapid oscillation of the string, resembling the sharp pointed R-wave of the cardiogram. This is usually of the diphasic type as the R-S-wave, though in occasional records, as in neuritis, it may even appear as quadriphasic. This wave which is deemed the true reflex action occurs in a very small fraction of a second after the blow is struck on the patellar tendon. Following this wave comes a wave or series of waves that are identical with the waves secured in the voluntary swing of the leg of equal length. Various factors, such as fatigue, drugs and toxic conditions in general, seem to influence the width of excursion of this reflex action, but the individual type of record remains constant and its relation to the inception of the oscillation due to the mechanical swing of the leg is the same. Certain cases show a positive initial deflection indicated by movement toward the upper right side of the records and usually of opposite polarity to the reflex itself. The reflex is of very short duration, about one-fortieth of a second. The mechanical swing of the leg usually begins one-tenth of a second after the reflex action and may consist of a single swing, or as many as five. The time element varies greatly in the swing in returning to the base line. If the subject holds the leg tense it is evidenced by a slower ascent and gradually receding descent of the marker to the base line. This has been termed, by old writers, the "inhibitory effect."

Clonus may be defined as a reflex, irregular contraction of muscles. In any muscle in an irritable stage with increased tonus, the tendency to clonus action is greater as the tone increases. The principal clonus described by clinicians are the ankle clonus, the patellar clonus and the jaw clonus. True clonus has the same significance as exaggerated knee jerk, and its relation to organic disease is most common in disseminated and lateral sclerosis.

Ankle clonus presents a definite record by the graphic method that will materially assist in a better understanding of the work. To the unaided eye all clonus appears alike, but records show that there are three distinct types. A constant record may be obtained not only showing the rate and frequency of the clonus but also its strength as recorded by the width of oscillations and also the duration, whether maintained for some time or quickly dropping off. The apparatus used in securing records of clonus consists of the arm band of a blood pressure apparatus fastened about the limb from which the record is desired. Tubing leads to the Marey tambour which replaces the recording apparatus used in securing the knee jerk. Slight inflation is made with the pump. The electrodes are used as in securing the knee jerk and are attached to the string galvanometer.

Tremors are rapid, minute muscular contractions with a rhythmic tendency. Tremor may appear in healthy individuals as well as in pathologic states. It may appear in normal individuals following physical exercises, mental agitation, cold, and so forth. Tremors are of two classes: intentional, that occurring during purposeful movement, and passive, that tremor persisting during rest. Putting the individual muscle group in action or under continued strain increases tremor. All tremors of the extremities are increased by extension and may be wholly absent when the patient is at rest. Most tremors are a spastic phenomenon and the centers are located above the reflex arc.

The tremograph was devised for making definite accurate records of tremors. It consists of two tambours set at right angles, and placed so that one is vertical and the other horizontal to the axis of movement. These tambours are connected with the tambours of the modified McKenzie polygraph by rubber tubing. The movement to be recorded is accentuated by the placing of spring vibrators of steel wire in front of the tambours. Metal olives with screw adjustment to permit their being placed in different positions along the spring vibrators, increase the oscillations and give a marked record of the vibration. Various handles are used to permit the securing of records from various parts of the body.

CONCLUSIONS

1. Graphic records of reflexes may be secured, showing the form of electric and mechanic response and also time elapsing between, (a) stimulus and electric response in muscle, (b) stimulus and mechanic response of parts, and (c) electric and mechanic responses.

2. In the normal reflexogram two elements are found: (a) An initial deflection of short duration, probably a definite reflex response. This appears to be present only in the records of electric response. (b) Definite responses due to muscular action. These show both in the records of electric response and mechanic response. These responses may be reinforced, for example, by Jendressik's method, or inhibited, for example, by psychic factors, producing probably a state of tension or resistance in the muscles involved.

3. Tonus plays an important part in the reflex act. Modifications may be due to an abnormal state in the afferent or efferent segments of the reflex arc and to conditions above the reflex arc.

4. In the reflexograms of abnormal individuals, the records may show modification of the reflex response (diminution, exaggeration, or perversion) due to altered conditions from fatigue, drugs, and pathologic conditions in the reflex arc and in the upper neurons.

5. These records are so consistent, definite, and permanent as to have a medicolegal value.

6. Irritability may be increased in varying degrees, and when this is sufficient, clonus may be produced. Clonus records show rate, amplitude, duration, response to increase of pressure by the manipulator, and fatigue.

7. Records of tremors show rate, rhythm, and amplitude. Tremors occur in normal individuals and in them are increased by voluntary movement. Tremor is modified in individuals, otherwise normal, by such factors as toxic states, fatigue, and drugs. In abnormal individuals alterations in rate, rhythm, amplitude, and effects of voluntary movement are recorded.

BRAIN CHANGES ASSOCIATED WITH PERNICIOUS ANEMIA*

HENRY W. WOLTMAN

The frequency with which symptoms referable to the central nervous system occur in anemic patients, particularly if the anemia is of the pernicious, or essential type, has long been recognized and made the object of extensive investigation.

Although the object of this study is the investigation of brain changes in essential pernicious anemias, it seems advisable to review some of the more important contributions to the literature on the changes found in the spinal cord in this disease.

Lichtenstern, in 1884, described two cases of pernicious anemia, complicated by spinal cord symptoms under the title, "Progressive pernicious anemia in tabetics." He considered the pernicious anemia to be dependent on the tabes, and it was not until 1886 that Lichtheim recognized the real significance of this syndrome. To him is due the credit of establishing the true relationship of pernicious anemia to subacute combined degeneration of the spinal cord, and of stimulating extensive research in this field, out of which a great many facts fundamental in neuropathology were crystallized.

While we now have a fairly clear idea of the pathologic processes involved, there still remain a great many problems which require further elucidation. This applies particularly to the understanding of the exact mechanism by which these changes are brought about. Although there are still some writers who consider the anemia to be the chief factor in causing the degenerations of the spinal cord (Goebel), most writers have come to the conclusion that it is really a toxin, or several toxins which must be responsible for these alterations (Minnich,

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The seven case histories, twenty illustrations, and the bibliography are herewith omitted.

Nonne, Petren, von Voss, Russel, Batten and Collier, Johnson, Reuling, Bonhoeffer, and others).

That toxins alone are able to produce such changes we know from the alterations that occur in the cord, which in many cases cannot be distinguished from the changes associated with pernicious anemia, when various poisons are introduced into the human organism. The same changes also appear as a result of certain poisons and in connection with certain morbid states; that is, tea (Gordon), lead, arsenic, ergot, pellagra, lathyrism, chronic alcoholism, diabetes, leukoemia, severe secondary anemias, diphtheria, Addison's disease, tuberculosis, syphilis, typhoid, carcinoma, senility, chronic jaundice, malaria, leprosy, influenza, scarlet fever, tetanus, pregnancy, and shock.

It was also pointed out that the nervous symptoms may precede the appearance of the anemia, sometimes by many months, which made the view that anemia alone might be the cause untenable (Minnich, Nonne, Bastianelli, Van Wart).

The fact that patients with pernicious anemia often have an elevation of temperature was also taken to indicate that a toxin was at work (Lloyd). von Voss, however, furnished the best evidence when he induced anemia in laboratory animals by injecting pyrodin, glycerin, pyrogallol, and toluylendiamin, with the result that only one animal showed cord changes, and these were different from the changes occuring in pernicious anemia; no changes, analogous to pernicious anemia in man, were found in these animals.

That the toxin, and not the anemia alone, is responsible for the cord changes, has thus become the generally accepted theory. On its source, nature, and mode of action, however, we are still completely at sea. If we were to accept Naegeli's view, that pernicious anemia is always a toxogenic anemia, coming from a variety of sources, notably such as the *Bothriocephalus*, pregnancy, syphilis, and malaria, and that pernicious anemia may in reality, at times, be a secondary anemia and amenable to treatment, the problem would become greatly simplified. Naegeli's definition, however, is not accepted by all writers, and many insist that a true pernicious anemia must be essential, or idiopathic, and some add, fatal, and that therefore, any demonstrable etiologic factor would at once place it in the class of secondary anemias. This leaves us in a difficult position. Nonne evaded this difficulty by substituting the term "lethal anemias." This looseness in the terminology should be kept in mind in reviewing the literature and in interpreting the necropsy reports. Thus, for example, again and again syphilis is found in cases reported under the caption "pernicious anemia;" the findings in such cases are obviously rather hazardous to interpret.

For this study, therefore, I have used only such cases of anemia as would be classed under the term "primary idiopathic." With this slight digression, I shall again briefly consider the theoretic toxin, or toxins, at work.

Minnich was the first to suggest that this toxin might be of gastro-intestinal origin; more recently attention has been directed to the tonsils and teeth.

Blankenhorn, in a clinical study of the blood serum of patients with pernicious anemia, made the observation that these patients, in whom the serum yielded the strongest Pettenkoffer reaction, showed, clinically, the greater involvement of the central nervous system. He, therefore, concluded that it is the presence of large amounts of bile salts in the blood that is responsible for such neurologic manifestations.

Our understanding of the mode of action of these toxins is little better. According to many authors one toxin is responsible for the blood vascular changes, so frequently observed, and for the neuronal degeneration (Johnson); others regard it as more selective in its properties, and consider this specificity, plus a difference in resistance, inherent in various structures of the central nervous system, as an explanation of the localization of the destructive process (Russell, Batten and Collier). Still others insist that there must be at least two separate and distinct toxins at work, one having an affinity for the red blood cells, the other, an affinity for the fibers of the spinal cord (Reuling). Von Voss, in discussing this phase of the subject, does not come to any such definite conclusions, but leaves the question *sub judice.* The changes may accordingly be due to (1) one toxin causing both the anemia and the cord changes; (2) a toxin being indirectly produced by the anemia, and bringing about the changes in the spinal cord; and (3) the anemia itself acting as a toxin, and through malnutrition causing the alterations in the cord.

The second hypothesis, in a slightly altered form, is also advanced by Bonhoeffer, who, in discussing the psychoses occasionally observed in patients with pernicious anemia, does not consider these specific reactions as due to a toxin, but believes other changes in the brain cells themselves or in their metabolism to be interposed; this is a view gaining increasingly wide acceptance in analogous conditions, as, for example, between alcohol and delirium tremens, as opposed to alcohol and drunkenness.

That the lesions found in the central nervous system are the result of toxin action can hardly be questioned; nor can it be doubted that anemia in itself can and does render the nervous elements more susceptible to the actions of these toxins. Any further statements are purely hypothetic and unwarranted on the basis of our present knowledge.

An animated discussion has centered around the pathologic mechanism instrumental in producing the so-called Lichtheim foci and the subsequent condition of combined sclerosis. According to the first theory advanced, the blood vessels through hyalinization, thrombosis, or rupture, were considered responsible for these lesions.

Minnich, in a series of five cases of pernicious anemia, free from neurologic symptoms clinically, and which subsequently came to necropsy, found no lesions in the nervous system other than multiple hemorrhages, which he studied in great detail. These he considered fundamental in the production of the Lichtheim foci, and believed them analogous to the multiple hemorrhages occurring in the retina, pleura, pericardium, intestinal serosa, and meninges. He assumed that the alterations taking place in the vessel walls themselves were initial in the perivascular lymph spaces and supporting tissue, with resulting lymph stasis, perivascular sclerosis, intimal thickening, vascular sclerosis, and consequent tissue destruction. Nonne's views were essentially the same.

The majority of writers, among them Burr, Bullock, Johnson and Marburg, mention vascular changes, such as proliferation and swelling of the intimal cells, hyalin degeneration, and often complete thrombosis, but their conclusions are not the same.

According to Marburg the localization of the pathologic process in the cord corresponds to the area which is best supplied by blood vessels, and hence has transported to it the largest amount of toxin. Curiously enough, Brauwer and Blaukwip reverse this statement, saying that not the areas best supplied with blood, but those most poorly supplied, are the ones which suffer most extensively. Schmaus, in this as in multiple sclerosis, is a supporter of the lymph-stasis theory.

While the "vascular theory" was for a time widely accepted, it did not long go unchallenged. It was pointed out that not only did the blood vessels in the diseased areas too often appear normal, but also blood vessels in healthy areas too often were much diseased (Bastianelli, Russell, Batten, and Collier, Jacob, Moxter, Von Voss, Putnam and Taylor). It was likewise shown that in a great many cases there was no evidence of hemorrhage (Russell, Batten, and Collier).

Relative to the lymph stasis theory, Lenel suggests that the swelling seen in the adventitial tissue may be only a stage in the "Abbauvorgang," and thus a result, rather than a cause, of the nerve lesions.

An entirely different explanation is advanced by Rothmann, who found hemorrhages, atrophy, and destruction of the anterior horn cells in the gray matter. These, he argues, as does Teichmueller, are the changes which initiate the cycle of disintegration, while the alterations seen in the white matter are due simply to a resulting secondary degeneration. He insists further, that although these lesions are not always demonstrable microscopically, the injury is there nevertheless, and the mechanism the same.

Goebel, on the other hand, though he also demonstrated changes in the gray matter, refutes this idea by saying that the changes in the gray matter are often missing, that the intensity and the localization of these changes do not correspond with those found in the white columns, and that in longitudinal sections, the commissural fibers are found to be intact. Additional evidence was supplied by Bastianelli, who noted that the white fibers were diseased only in the peripheral portions of the cord and that the gray matter, for this reason, could not be the primary seat of the degeneration.

On account of the evidences of inflammation sometimes observed, and the occasional febrile course, it is believed by some (Boedeker and Juliusberger) that the process taking place here is really a true myelitis of the disseminated type. This, Nonne believes is also true of sepsis and senility. The fact, however, that inflammator reaction, such as cell infiltration, is too often lacking, and that the gray matter is only exceptionally involved (Billings) argues against this view.

Edinger, in support of his "Ersatztheorie" performed an experiment which has a direct bearing on the point under consideration. In the spinal cords of a number of rats, in which he produced an anemia and which he then set to work by the ingenious device of suspending them by their tails, he found extensive degenerative changes, while in the cords of control rats, which were not anemic, no such changes could be detected.

Finally, Dana has emphasized two other factors, which may be at work in this disease and which may be instrumental, first, in determining the characteristic localization, and, second, in deciding which patients are to get a combined sclerosis, and which are to remain altogether free from it. It is in reality the peripheral ends of the axones of the pyramidal cells and of the posterior ganglion cells that bear the brunt of the destructive process; this, he says, may be due to the distance of this portion of the nerve fiber from its trophic center. Relative to the second point, he suggests that this may be explained by individual predisposition; that persons hereditarily endowed with "weak cords" will suffer from a complicating cord degeneration, while those who are not so predisposed, will escape.

Cavity formation is not an infrequent finding in the spinal cords of patients with pernicious anemia. (Baumler, Camac and Milne, Bullock, Friedlander, and Henneberg). Boedekér and Juliusberger described peculiar staff-like structures associated with a few of the anterior horn cells; these were at times scattered throughout the entire cell, at times in only a portion of it, again partly within the cell and partly in the pericellular space, and sometimes entirely within the latter. These structures, stained green with iodin, red-brown with basic fuchsin, were present in the Marchi sections, and remained unstained with methylene blue, eosin and hematoxylin.

The foregoing is a rather fragmentary and disconnected review of this aspect of the pathology of pernicious anemia, but it is not my object in this paper to enter on a discussion of the many theories advanced save only so far as may be necessary to explain the pathologic changes noted in the cortex.

The literature bearing on the clinical manifestations of cortical origin is not so voluminous as is that concerning the spinal cord; however, in recent years, attention has been directed this way, and numerous cases, in which psychotic manifestations were noted, have been placed on record. Addison, in 1855, when he first described the disease, spoke of the occasional wandering of the mind, and, indeed, a terminal delirium, usually of a mild type, is one of the commonest of the mental phenomena noted. There appears to be no law according to which these disturbances develop, and the psychic alterations may run the entire gamut of mental symptomatology.

Patients who develop some of the better defined types of psychoses, such as manic depressive insanity, probably have an individual predisposition, the pernicious anemia being really more or less independent of the mental disorder; when this has not been the case, however, the majority of writers have come to the conclusion that the individual may be altogether free from any neurotic tendency, the psychosis being then placed in the category of the exhaustion (Bonhoeffer, Meyer) or infection-intoxication psychoses (Siemerling).

Putnam and Taylor consider a neurotic tendency fairly common; they noted in their patients, as a rule, an exaggeration of native traits. Church describes the mental condition as one of a continuation of the dream state, which these patients cannot shake off on being roused and which usually subsides spontaneously on further stimulation. Pickett, from a study of seven cases, gives the composite mental picture of these patients, as a shallow confusion with impairment of ideas of time and place, increasing on awakening from sleep; illusions, particularly of identity, are common. Hallucinations and persecutory delusions may arise. "The pernicious anemia is mainly an abeyance of the mind." Very often the psychosis may simulate a general paresis (Marcus, Camp); Korsakow's syndrome has also been noted following a delirious condition (Bonhoeffer).

Just as cord symptoms may appear long before there is any evidence of the underlying pernicious anemia, so mental symptoms may appear in persons who may be somewhat anemic, but in whom the diagnosis of pernicious anemia would not be warranted. This was well shown in a case reported by Marcus, and also emphasized by Langdon, who in a series of patients, some having definite pernicious anemia, others having more or less severe anemia, designated the condition as "pre-pernicious anemia." Likewise, these symptoms are strikingly transitory, and usually improve, *pari passu*, with an improvement in the physical state (Grawitz).

Kraepelin, although he discusses the relation of anemia to psychoses at some length, does not mention pernicious anemia in particular, and concludes by saying that it is not clear whether the anemia is a causative factor or an accidental accompanying condition.

The contributions of Barrett are particularly illuminating. Among 650 necropsies on insane persons in Michigan, he reports that there were fifteen cases of pernicious anemia, and suggests that this disease may play a larger rôle in psychiatry than is now supposed. In his first study of nine cases, two resembling dementia præcox, one manic depressive insanity, and six asthenic with paranoid features, he concluded that, as a whole, these patients had in common irritability and suspiciousness, which formed the groundwork for delusions of persecution, the content of which was generally influenced by the somatoneurologic symptoms. In several cases hallucination and confabulation occurred, suggesting a Korsakow's psychosis. There was no marked deterioration, and comprehension and orientation were usually clear, except for a rare episode. In two instances there was slight expansion. In a number of cases there were remissions in the mental condition which can parallel with those on the physical side. In all but one there was hereditary predisposition, which he regards as of considerable importance. He classifies these cases among the paranoid conditions which are symptomatic of a toxic-organic process affecting the central nervous system, analogous to conditions found in tabes, alcoholism, and certain drug intoxications.

Only a few of the cases reported present symptoms referable to other parts of the central nervous system, outside the cord. Among these optic atrophy stands first and has been several times noted (Russell, Bastianelli, Putnam and Taylor, Bramwell). Collier, however, declares it to be a decidedly uncommon occurrence, having been found but once in fifty-eight cases, and in this one instance being probably of syphilitic origin.

Various attacks of cortical origin have been described, such as a sudden feeling of cold and death in an extremity (Eichhorst), light hemiparesis of the face (Immermann), passing hemiplegic attacks (Mueller, Nonne), which may be accompanied by convulsive seizures (Mueller and Bierner), diplopia (Russell, Batten, and Collier), sudden severe headaches (Hawthorne), and total blindness from extensive softening of the occipital lobes (Wicher).

Comparatively little has been published concerning the pathologic lesions found in the brain itself. Birulja, in 1894, found numerous small blood extravasations, accumulations of lymphoid cells, pigment masses, and diminished tincture with carmin. Ransohoff noted inflammatory foci in the brain and cord. Mott described marked changes in the corticopyramidal cells, and on examination with the Marchi method, showed degeneration in the whole pyramidal system, from the crotex downward. Spiller, however, takes exception to this diagnosis and looks on it as a case of amyotrophic lateral sclerosis, associated with anemia. This author found changes as high as the middle of the pons, which he considered retrograde. Preobrajensky has described two types of foci occurring in the medulla, cord, and cerebellum, one, miliary sclerotic foci accompanying the blood vessels, and two, miliary foci from disintegregation of the nerve substance.

Schroeder regularly finds miliary foci occurring in the brain in lethal anemias, not found in other diseases. These differ somewhat from the Lichtheim foci and are usually about 80 microns to 100 microns in diameter, globular or slightly oblong, always isolated, and generally widely separated from each other; they are in close relationship to the blood vessels, each one having a capillary in its center, and display no selective localization. They are most readily found in Nissl-stained sections, in which the center appears clear, containing sometimes a few blood cells, and the periphery blue, being made up of more or less degenerated glia cells. These "Ringwallherdchen" have no relation to plaques found in the spinal cord.

Barrett has reported findings in eleven cases, which are exceedingly interesting. The Nissl bodies he found to be often markedly disintegrated, a few cells showing the characteristic axonal degeneration. The neuralgia cells were, as a rule, moderately increased and had a tendency to group arrangement; in some of them mitotic figures were noted. Rod cells and cells of odd shapes were present in the cortex in considerable numbers. Degenerative changes in the blood vessels and pigment deposit were common. The striking finding, however, was that of typical Lichtheim plaques in four of the eleven brains examined, ten of which showed distinct pathologic changes. These changes, he concludes, were such as occur in conditions of chronic intoxication and resemble those found in chronic alcoholism. He also found in one of the brains (Case 2, M.T.) the foci described by Schroeder.

Pfeiffer, in a very careful histologic study of the cortex, found many cellular changes, the most frequent of which was swelling of the ganglion cells, invariably associated with hyperpigmentation. These changes are similar to those found in psychoses of toxemic origin.

DISCUSSION

Certainly it cannot be said that the cortex of pernicious anemia patients is barren of pathologic findings. The lesion of prime interest is, of course, the occurrence of plaques in the medullary substance of the cortex, which in every respect resemble the lesions so often found in the spinal cord. In the cases reported by Barrett there was a very marked mental disturbance associated with the pernicious anemia; this obtains in only one case of my series, the mental condition of the patients in the remainder being no more altered than is usually seen in pernicious anemia. In three of the seven brains studied, this focal degeneration could readily be seen with the naked eye, in two it was of moderate intensity, requiring a microscope for its detection, and in two it was very slight indeed, only a very few small areas having been noted.

The incongruity between cases presenting cord symptoms clinically and those showing pathologic changes at subsequent examination has long been a matter of comment; thus, also, in Case 4 there was marked clinical evidence of cord involvement, while pathologically there appeared only a very slight degeneration as shown in the Weigert sections, although in the Marchi sections this change was more evident. On the other hand, in the same case the mental symptoms were very slight and no change in the mentality appeared until just preceding death, while the degenerative changes in the brain were very marked. If one considers only those cases in which a definite psychosis existed this lack of correlation between the clinical and pathologic findings is even more striking. Although Barrett found definite pathologic changes in ten of the eleven cases which he reports, the Lichtheim plaques were present in only four, and very insignificant in the mental case here reported; on the other hand, in four of the seven cases of this series, the degeneration was very marked, while the mental symptoms were no more marked than is ordinarily observed in pernicious anemia. Just what part these lesions play in the production of this mental condition cannot be definitely stated. As Barrett and others have shown, the development of well marked psychotic manifestations is probably independent of the pernicious anemia itself. The same lack of causal relationship between the mental symptomatology and the pathologic changes observed, probably obtains with reference to these plaques also. It is not at all unlikely, however, that they may aid in the production of the indifference, irritability, apathy, and somnolence so frequently seen, although the principal factor underlying these phenomena is probably the toxin itself.

The percentage of pernicious anemia cases showing pathologic lesions in the cord is rather high, although an accurate figure cannot be given. Nonne, in a series of seventeen cases, found cord changes in ten, about 59 per cent. Minnich, in thirty cases, found changes in twenty-three, about 77 per cent; Petrèn, in nine cases, found changes in two, about 22 per cent. In the five cases of my series in which the spinal cord could be studied, combined sclerosis was marked in three, moderate in one, and very slight in one. In comparison it will be seen that the degenerative changes in the medullary portion of the cortex occur fully as often in pernicious anemia, if not oftener, than do changes in the spinal cord, although the lesions in the brain are usually smaller, fewer in number, more widely scattered and not so readily enlarged by confluence and secondary degeneration, which renders their detection more difficult. In Cases 1, 2, and 3 there was a well marked change in both the brain and the spinal cord; in Case 4 the changes in the brain were marked while those in the spinal cord were relatively slight; in Case 5 the degeneration of the brain was very slight while that in the cord was moderate. If the results of such a small series of cases can be used in formulating a general principle, it might be said that the changes in the cord and in the brain run fairly parallel.

Of not less importance, however, are the smaller areas which were described in the Weigert sections as being more or less circular in outline, about 0.1 mm. in diameter, and most numerous in the medullary portion of the cortex, just underlying the marginal gray of the convolutions. The same areas appeared in other slides as localized patches in which the fibrillar structure was more or less pushed aside, the meshes being thereby enlarged; the margins were not well defined, but graded almost insensibly into the surrounding tissue, the entire structure presenting a picture such as might be brought about by a localized edema. As serial sections showed, they may be unrelated to any blood vessels, although as a rule they tend to surround these like a halo. Axis cylinders passing through these areas were found to be more or less disintegrated, and in the center of a number of them was seen an accumulation of granular debris, (as shown in figure). There was no evidence of any associated glia reaction or cellular increase. In a number of instances these meshes were found to be more or less distended with a somewhat hyaline, usually basophilic substance, which resembled in every respect material found in the perivascular spaces, and with which it at times seemed to be continuous, as though it had been pressed into the tissues There appears to be but one conclusion, and this is the obvious one, which is that at least some of the white fibers, including the myeline sheaths and the axis cylinders, are destroyed, presumably through toxic action, possibly assisted by stasis, by a substance which accumulates in the so-called perivascular space. The very marked degeneration seen around some of the vessels in the Marchi sections, as well as the Weigert sections, supports this theory as additional evidence. It was also noted, however, that these perivascular structures were not the only ones in which this degeneration was initiated, but that a very difluse and widely scattered destruction of the medullary substance at times occurred. To state that this is due directly to toxin action is rather arbitrary, though it certainly appears by virtue of its apparent simplicity to be the case, and it is not only possible, but also probable, that such a mechanism may obtain.

There is another factor, however, which the study of this material shows to be instrumental also in bringing about degeneration in the medullary substance of the cortex. In Cases 2, 3, 6, and 7 certain areas of pallor, resembling very closely those just referred to, were also present in the marginal gray matter of the gyri. In perhaps the majority of instances they were found surrounding a pyramidal cell, the cell thus located presenting all degrees of degeneration from one which was practically normal in appearance to one which was completely disintegrated, the cells in the vicinity being practically normal as revealed by microscope. It seems indisputable that this cellular disintegration and the surrounding area of partial necrosis bear some relation to one another. The interpretation of this, however, is not simple. We are probably justified in assuming that the process at work does not differ materially from that which brings about degeneration in other structures of pernicious anemia brains. Accordingly, this cellular destruction is probably the result of the action of some toxin, assisted possibly by some nutritive factors of mechanic origin. The manner in which this toxin is conveyed to the cell is probably the same as elsewhere, namely, through the lymphatic channels; incidentally this hypothesis would serve as additional evidence of the existence of a so-called pericellular space of Obersteiner. Granting that pyramidal cells of the cortex may be thus destroyed, a secondary degeneration of the axon would then follow which would account for at least some of the degenerating fibers seen in the cortical white matter.

Certain other cell changes were observed also, although, on the whole the cells were practically normal in appearance. Among the changes seen, were varying degrees of tigrolysis, particularly in the cells of the second and third pyramidal layers, vacuolization, loss of cell processes, indistinctness of the cell outline, eccentric positions of the nuclei and of the nucleoli, some of which were very much swollen, deep staining of the nucleus, partial extrusion of the nucleus, and in two cases, definite axonal reaction. Satellitosis and neuronophagia were observed also. Fuchsinophilic granules were seen in the cells of a number of cases. In certain cells there appeared to be an increase in the amount of intracellular pigment which exceeded the normal; on the whole, however, this was not the case.

Relative to the glia changes, little can be said. There appeared to be in some of the cases a little increase in the coarser glia fibers, which often seemed enlarged, nodular, and very wavy. Henneberg's observation, that there is in general little glia reaction in cases of this kind, owing possibly to the poor nutritional state, would seem to be borne out by these findings. Too much cannot be said in praise of Ramón y Cajal's comparatively new gold stain for glia cells and the coarser glia fibers. We found it to yield very excellent pictures.

Hemorrhages were noted in but one case, and here they were not very numerous. Definite softening was observed in two of the cases, in one involving a portion of the basal nuclei, and in one, the cortical white matter. The "Ringwallherdchen" described by Schroeder as being so characteristic of pernicious anemia brains, although carefully sought, could not be found, but it seems that this should be no difficult task, in view of his description. Only one focus, in which the resemblance was, as a matter of fact, exceedingly remote, was found which could possibly be interpreted as an accumulation of disintegrated glia cell nuclei.

SUMMARY

1. Not only do degenerated areas of the Lichtheim type, such as are typically found in the posterior and lateral funiculi of the spinal cord in pernicious anemia patients, occur in the medullary portions of the brains of these cases, but they occur with about the same frequency, although their demonstration may be rendered more difficult.

2. Patients who show degenerative changes in the spinal cord at necropsy, usually show the same type of lesion in the brain also.

3. In addition to these focal degenerative areas found in the white matter, which may or may not be associated with blood vessels, we also find a diffuse degeneration. This although somewhat more striking in the long association tracts, also occurs in the short commissural fibers passing from one gyrus to another, thus rendering the view untenable that it is the distance of these fibers from their trophic centers which is instrumental in causing the degeneration.

4. The gray matter is by no means immune from the destructive process. This is usually focal in character, and begins around the pyramidal cells of the marginal gray layer, the cells themselves being ultimately destroyed in the process which, in turn, gives rise to a secondary and very diffuse degeneration of the medullated fibers in the white matter.

5. Although some degeneration was noted in the fibers of the internal capsule and in the long tracts passing through the pons, the degeneration at this level was less intense than that seen either in the cord or in the brain.

6. The appearance of these plaques, not only around the blood vessels but also around some of the larger pyramidal cells, seems additional evidence that lymph stasis is an important factor in the production of these foci.

7. Well marked psychoses, such as are occasionally associated with pernicious anemia, probably have little or nothing to do with these destroyed areas.

8. The milder mental manifestations such as somnolence, apathy, and terminal delirium, are probably in a measure dependent on these lesions, although the chief causative agent of these symptoms is probably the toxin itself.

VIII

HEAD, TRUNK, AND EXTREMITIES

THE GROWTH OF THE FETAL HEAD FROM THE OBSTETRIC VIEWPOINT*

LEROY A. CALKINS

This study on the prenatal changes in the form and dimensions of the fetal head is one of a series of studies undertaken with the idea of determining the nature of general body growth in fetal life, and of perfecting a method of determining the exact size of the fetus in utero.

Three hundred thirty-nine selected specimens ranging from 23 mm. to 544 mm. in total, or crown-heel, body length were studied. All of the specimens were preserved in formalin. Measurements, as follows, were taken on each: (1) the total, or crown-heel, length, (2) the sitting, or crown-rump, length, (3) the suboccipitofrontal diameter, (4) the suboccipitobregmatic diameter, (5) the occipitofrontal diameter, (6) the occipitomental diameter , (7) the biparietal diameter, the occipit the occipitomental diameter, (8) the occipitofrontal circumference, (9) the suboccipitofrontal circumference, (10) the sub-occipitobregmatic circumference, (11) the occipitomental circumference, and (12) a circumference designated as the "large circumference" which was taken around the mentum and superior tip of the occipital bone. These measurements were arranged in 5 cm. intervals of crown-heel length, and field graphs based on the total length were constructed for each. From these graphs and averages curves were plotted by the method of arithmetic averages for each of the several measurements listed.

These curves and graphs bring out the fact that during the early and middle part of the fetal period all of the dimensions studied are first degree functions of the total length of the body or, each dimension when plotted against total body length appears as a straight line. Therefore these dimensions may be expressed in terms of the total body length by simple empirical formulas having the general form

$$Y = KX \pm K'$$

Where Y is the dimension in question expressed in millimeters, X is the total body length expressed in millimeters and K and K' are certain definite constants peculiar to the dimension. Since these dimensions all follow this simple law of relative growth they are exactly proportional to one another and it is possible to deduce one of them from another by simple arithmetic calculation.

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Apparently another factor comes into play in late fetal life, as each curve, except those in the occipitomental plane, undergoes a deflection toward the horizontal at its upper end.

From the study of these curves, graphs, and formulas the following conclusions are drawn:

1. The inclination or grade of the curves representing diameters or circumferences in the occipitomental plane is steeper than those of other planes, that is, the rate of growth of the base of the skull plus the lower jaw is more rapid throughout fetal life than is the growth in other planes.

2. The large circumference, which throughout the greater part of fetal life greatly exceeds the other circumferences, is shown to be smaller than the others, except possibly the occipito-mental circumference, in very early fetal life. The same may be said of the occipito-mental diameter with reference to the other diameters.

3. It may thus be seen that early in fetal life the head is roughly spherical and later assumes an ovoid form. This substantiates in some degree the work of Sergi, Tovo, Frassetto and others on the form of the fetal skull.

4. No two curves possess the same "grade" up to the point of divergence toward the horizontal, that is, each diameter or circumference has its own peculiar rate of growth. Above the point of divergence, however, a very marked tendency of the curves to run parallel with one another is noted. An exception is found in the case of the suboccipitobregmatic diameter after it has taken a second deflection toward the horizontal between 41 cm. and 42 cm. crown-heel length. This tendency to parallelism might be explained in either of two ways, (a) the fetal head attains its newborn shape at some time between the fifth and seventh months, and its growth thereafter is in size only in contradistinction of its earlier changes in both form and size, or (b) the fetal head is compressed into shape that will most readily admit of its passage through the birth canal, as has been long taught and thoroughly believed. These factors will be considered at length in a later publication.

THE FETAL DEVELOPMENT OF THE NASAL CAVITY AND NASOPHARYNX*

FRANK N. KNAPP

This investigation of the growth and proportions of the nasal cavity and nasopharynx in prenatal life was based on a study of 117 fetuses in the collection of the Department of Anatomy of the University of Minnesota. These specimens, which were preserved in formalin, ranged from 5.4 cm. to 55.0 cm. in total or crown-heel length. The head of each specimen was carefully split in the median sagittal plane and a series of twenty-nine selected measurements of the various structures of the nasopharyngeal region were made from it. Median sagittal tracings were also made of each specimen and in forty-one instances casts of the nasal cavity and nasopharynx were made in Wood's metal. After all measurements were completed they were averaged by 5 cm. intervals of crown-heel length and from these averages curves were plotted of the growth of the various parts under consideration.

The chief facts brought out by this study are:

1. The hard palate, the cribriform plate, and the nasal septum grow in length at approximately the same rate throughout fetal life. The soft palate increases in length much more slowly and irregularly than the hard palate.

2. During fetal life the nasal cavity elongates much more rapidly than it increases in height or breadth. The height of the anterior part of the cavity grows more rapidly than the height of the posterior part.

3. The rates of growth of the several nasal meatuses differ considerably. The middle meatus increases the most rapidly, its rate of growth corresponding very closely to that of the nasal fossa as a whole. The superior meatus grows slightly more slowly and the supreme meatus distinctly more slowly than the middle meatus. The inferior

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meatus hardly increases in height during the latter part of the fetal period although it grows considerably in length.

4. The nasal conchæ grow much more rapidly in length than in height before birth. When arranged according to the rapidity of growth in length they fall in the following order: inferior, middle, superior, Suprema I and Suprema II. When arranged in accordance with their rapidity of growth in length they are in the following order: middle, inferior, superior, Suprema I and Suprema II.

5. During fetal life the width of the nasopharynx, the length of the posterior margin of the hard palate, and the length of the soft palate all increase at approximately the same rate.

6. The orifice of the auditory (eustachian) tube gradually shifts backward from the posterior margin of the hard palate during fetal life, but the opening remains at the level of the floor of the nasal cavity from the third fetal month until birth.

SOME GROWTH CHANGES IN THE WALLS OF THE THORAX OF THE HUMAN FETUS*

CHARLES K. ROYS

This study deals primarily with the changes in form and size of the walls of the thorax in fetal life. While the observations were made mainly in the study of the human fetus, a number of observations were made on the form of the thorax of embryos and of specimens of adults of a number of species of animals. The results obtained may be summarized as follows:

The changes in the anterior chest wall in embryonic life are very marked and seem dependent primarily on the modifications in the form and relations of the thoracic and the upper abdominal viscera (particularly the liver and the heart). In the fetal period, after the cartilaginous thoracic skeleton has been established, the anterior chest wall increases greatly in size but its form remains almost unmodified.

In the early prenatal life of man the thoracic index is very high, a characteristic which may be attributed to the great anteroposterior diameter of the heart and liver in this period. With the development of the cartilaginous thorax the index drops rapidly, and after the second month the chest appears circular in cross section or is slightly flattened anteroposteriorly. The cylindric type of thorax is found to be characteristic of the fetuses of various animals (sheep, pig, rat, mouse and cat) as well as of the human fetus.

A comparison of the thoracic indices of a number of adult mammals of widely separated species showed no evidence of a phylogenetic evolution towards the anteroposteriorly flattened type of thorax typical of the human adult. The thoracic index is apparently closely associated with the habits of life of the animal. Mammals which climb, burrow, fly, or swim have low indices comparable with that of man. Wide differences in the thoracic index are encountered in different varieties of the same species when these varieties have adopted different habits of life. These differences are particularly noticeable in the varieties of domesticated animals.

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BÁRÁNY TESTS IN SUPRATENTORIAL TUMORS PROVED BY OPERATION OR NECROPSY*

HORACE R. LYONS

INTRODUCTION

A slow but sincere scientific interest, a steady increase in knowledge, and an indefinite amount of discussion, are embodied in neuro-otology in general and in the Bárány tests in cases of supratentorial tumor in particular. Formerly neurologists looked on neuro-otologic localizations of intracranical lesions with interest but also with reservation. These limitations are being eliminated and will be steadily eliminated as our knowledge from proved cases multiplies. The localization by Bárány tests of supratentorial tumors is one of the later developments of neuro-otology.

A Bárány test is indicated in all cases of vertigo, but is especially useful in all lesions of the central nervous system. In performing this test it is essential that the turning and the caloric tests are not made consecutively because the responses are modified after repeated stimulations of the semi-circular canals. It is also useful for productive work, that the intracranial localization of a lesion by this test is made independently and without knowledge of the neurologic localization. A report of nine cases in which the test was made follows:

REPORT OF CASES

Case A236828. Miss S. L., aged 40, was examined July 2, 1918, chiefly because of dull frontal headaches and loss of strength. The patient's family and personal history are negative. The patient had always been well until one morning in October, 1917, while combing her hair she felt a sudden jerk in the left arm and it immediately became numb and powerless. Severe and almost continuous frontal headaches began at this time. Projectile vomiting often followed the headaches and somewhat relieved them; the left hand improved slightly. Partial deafness, which had existed since childhood, increased. The patient's limbs jerked when she was lying down.

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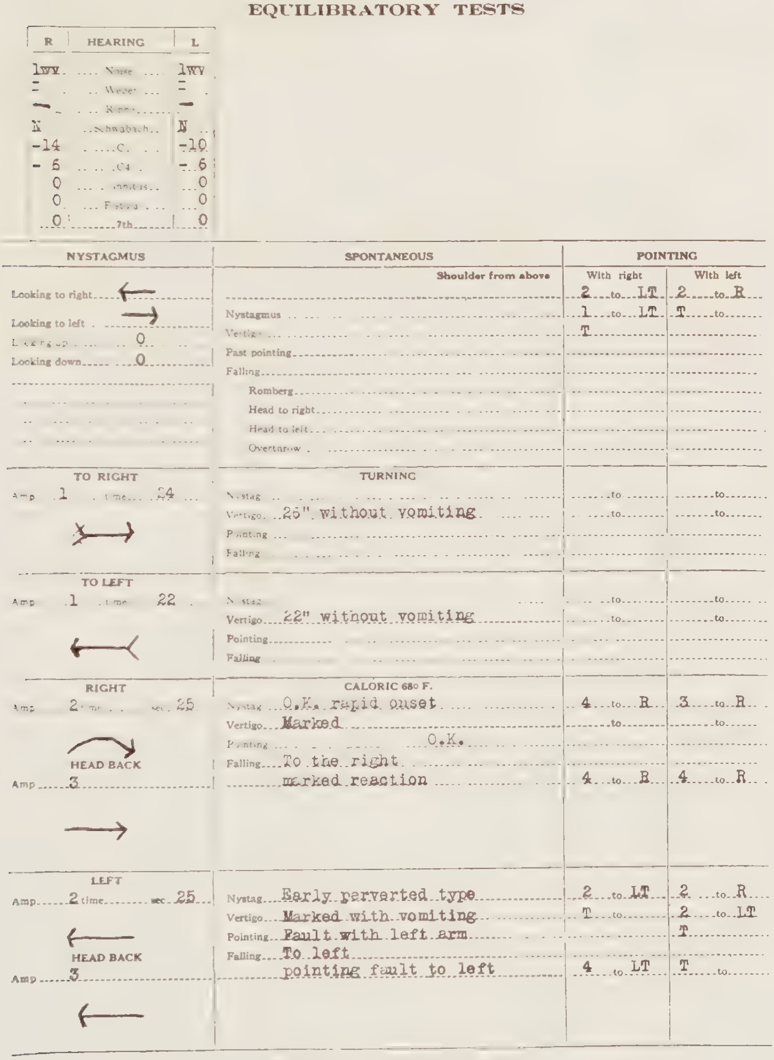
Physical examination.—The weight, blood pressure, urine, and blood counts were normal. The eyes showed double choked discs of three diopters. The blood Wassermann test was negative. The spinal fluid Wassermann tests with 0.4 and 0.5 c.c. were negative. The Nonne reaction was positive.



EQUILIBRATORY TESTS

R	HEARING	L
1wv	Noise	1wv
=	Weber	=
—	Rinne	—
N	Schwabach	N
-14	C	-10
-6	C4	-6
0	Tinnitus	0
0	Fistula	0
0	7th	0

NYSTAGMUS	SPONTANEOUS	POINTING	
	Shoulder from above	With right	With left
Looking to right ←		2 to LT	2 to R
Looking to left →	Nystagmus	1 to LT	T to
Looking up 0	Vertigo	T	
Looking down 0	Past pointing		
	Falling		
	Romberg		
	Head to right		
	Head to left		
	Overthrow		
TO RIGHT	TURNING		
Amp 1 time 24	Nystag	to	to
	Vertigo 25" without vomiting	to	to
→	Pointing		
	Falling		
TO LEFT			
Amp 1 time 22	Nystag	to	to
	Vertigo 22" without vomiting	to	to
←	Pointing		
	Falling		
RIGHT	CALORIC 68° F.		
Amp 2 time sec 25	Nystag O.K. rapid onset	4 to R	3 to R
	Vertigo Marked	to	to
↷	Pointing O.K.		
HEAD BACK	Falling To the right		
Amp 3	marked reaction	4 to R	4 to R
→			
LEFT			
Amp 2 time sec 25	Nystag Early perverted type	2 to LT	2 to R
	Vertigo Marked with vomiting	T to	2 to LT
←	Pointing Fault with left arm		T
HEAD BACK	Falling To left		
Amp 3	pointing fault to left	4 to LT	T to
←			

CHART 1. Case A236828.

Neurologic examination (July 4, 1918).—The neurologic examination was rendered difficult by the somewhat clouded mental condition of the patient. A nystagmus was noted. The cranial nerves were otherwise practically normal, with the exception of bilateral choked discs of about three diopters. Movements of the left arm were awkward as compared with those of the right. The reflexes were normal throughout, save for a slight diminution of the left abdominal reflexes. With the exception of a moderate loss of joint sensation of the left toes and an almost complete loss of joint sensibility in the left fingers, with corresponding asterognosis, sensation was normal throughout. No other significant changes were noted. A neurologic diagnosis of a tumor of the brain, located probably in the post-central gyrus of the right side, was made.

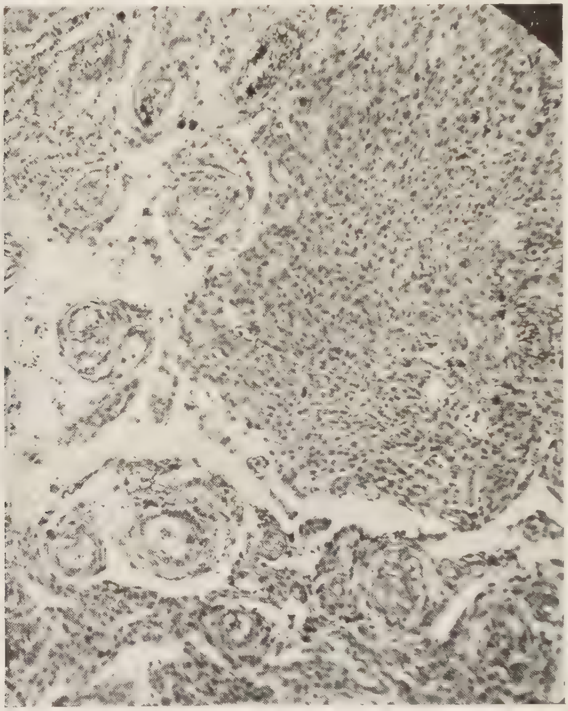


FIG. 168 (Case 236828).—Photomicrograph of glioma from the right frontomotor area of the brain. × 100.

Bárány test.—A bárány test revealed a moderate combined type of deafness, a bilateral spontaneous horizontal nystagmus, and a spontaneous pointing fault with the left arm. The turning test showed prompt reactions throughout. The caloric test revealed, on the right, a marked and definite exaggeration of all responses from all the canals. Nystagmus began almost at once; with the test of the left verticles it was of a perverted type, with vomiting and marked vertigo which was early and severe on the right also. A pointing fault was exhibited by the left arm. Falling was to the left. The horizontal canal showed marked reactions throughout. The reactions from the left canals, which showed interference with the posterior longitudinal bundles and the middle peduncle on the same side, were interpreted as pressure signs. The diagnosis from the Bárány test (Chart 1) was a supratentorial lesion on the right side causing pressure downward.

July 16, 1918, a glioma of the brain 5 by 10 cm. weighing 63 gm. (Fig. 168) was removed from the right frontomotor area.

January 16, 1920, when the patient returned for examination she was normal mentally and had control of the left arm.

Case A235175, Mrs. R. P. O., aged 47, came to the clinic June 14, 1918, walking, but in the need of considerable support. The patient's father died of an accident; her mother is 78 and in good health. Two brothers are in good health and two died of typhoid fever and scarlet fever respectively. One sister is well. One daughter, sixteen months of age, died of sarcoma of the kidney. The patient's menstrual history was not unusual. The last period was in March, 1918; previous illnesses were also unimportant. Her chief complaint was inability to walk for the past two and one-half years. She felt physically weak and mentally tired. Eight months' rest in a sanatorium had not especially benefited her. She had intense bilateral frontal and occipital headaches. Early in December, 1917, the patient was in coma for three days, then became markedly apathetic and entirely lost her memory for past incidents. At the time of examination she did not remember going to a sanatorium. Early in the spring she again went to a sanatorium for six weeks and was somewhat improved, but on returning to her home her condition became worse. She had involuntaries and urinary frequency with loss of control of the sphincter.

Physical examination.—The patient's weight was 175 pounds, 30 pounds above normal. Her left pupil was larger than the right. She had a double choked disc of about three diopters right and one to two diopters left. There was moderate blurring and loss of detail about both discs. Reflexes were normal. The Wassermann and Nonne tests on the spinal fluid and the Wassermann test of the blood were negative. The lymphocytes were normal. The routine urine and blood examinations and the combined phenolsulphonephthalein test were all negative. A roentgenogram of the head showed an apparent thickening of the base of the sella with obliteration of the posterior clinoid process.

Neurologic examination (June 14, 1918).—Neurologic examination revealed the following status: Vision was 6/6 in both eyes; there was a moderate blurring and loss of detail around the edges of both discs, suggesting a pupillitis; the visional fields were practically normal. The left pupil was slightly larger than the right, with slight impairment of reaction to light in the former, and considerable impairment in the latter; reaction to accommodation was normal. There was a nystagmus on looking toward the right. The tendon reflexes were all moderately increased; the abdominal reflexes could not be elicited; however, the patient was obese and the abdominal walls flabby. The patient walked on a rather wide base and gave the impression of being very feeble. There appeared to be some dementia; the patient asked the same questions repeatedly, raised numerous objections to the examinations and coöperated very poorly. The spinal fluid tests were negative.

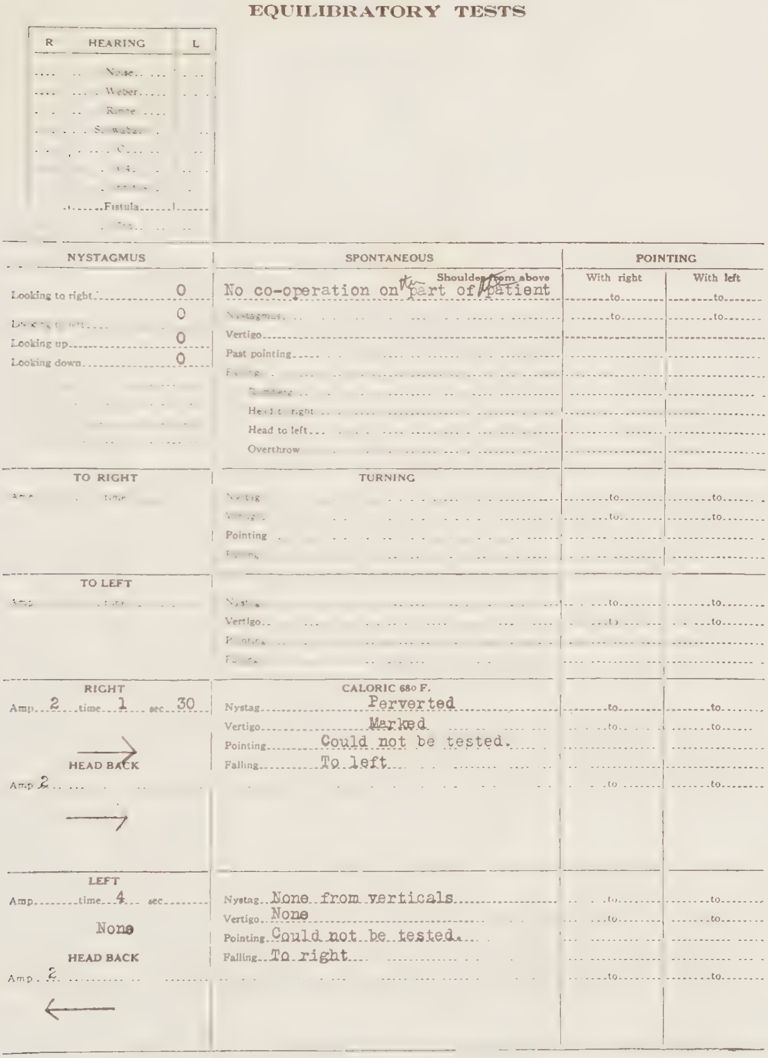
The patient was sent home to be cared for by a local doctor and asked to report by letter frequently. Her condition became definitely worse; when she returned Jan. 31, 1919, projectile vomiting was more frequent than at the time of the first examination, consciousness was decreased, and double choked discs were increased to four diopters.

Neurologic examination (Jan. 31, 1919).—There were now definite bilateral choked discs and a nystagmus. There was a marked general weakness, particularly on the right, with a corresponding increase in muscular tonicity. The tendon reflexes were all greatly increased, the abdominal reflexes were absent, and there was a strongly positive Babinski phenomenon on the right and one doubtfully positive on the left. The mental condition was decidedly clouded, attention being too poor to make a detailed examination.

A diagnosis of brain tumor, probably located in the left frontomotor area, was made.

Bárány test.—The Bárány test presented one of the interesting phenomenon syndromes of supratentorial tumors (Chart 2). There was no cochlear fault in either ear, nor was there any spontaneous nystagmus. The patient was in the hospital under observation.

She was unable to raise her arms, due mostly to her demintia, but somewhat also to her weakness. A turning test, therefore, was impossible.



EQUILIBRATORY TESTS

R	HEARING	L
	Noise	
	Weber	
	Rinne	
	Schwabach	
	C[illegible]	
	[illegible]	
	[illegible]	
	Fistula	
	[illegible]	

NYSTAGMUS	SPONTANEOUS	POINTING	
	Shoulders from above	With right	With left
Looking to right 0	No co-operation on the part of the patient	to	to
Looking to left 0	Nystagmus	to	to
Looking up 0	Vertigo		
Looking down 0	Past pointing		
	Falling		
	Romberg		
	Head to right		
	Head to left		
	Overthrow		
TO RIGHT	**TURNING**		
Amp time	Nystag	to	to
	Vertigo	to	to
	Pointing		
	Falling		
TO LEFT			
Amp time	Nystag	to	to
	Vertigo	to	to
	Pointing		
	Falling		
RIGHT	**CALORIC 68° F.**		
Amp 2 time 1 sec 30	Nystag Perverted	to	to
	Vertigo Marked	to	to
→	Pointing Could not be tested.		
HEAD BACK	Falling To left		
Amp 2		to	to
→			
LEFT			
Amp time 4 sec	Nystag None from verticals	to	to
None	Vertigo None	to	to
	Pointing Could not be tested.		
HEAD BACK	Falling To right		
Amp 2		to	to
←			

Chart 2. Case A235175.

Two features were prominent in an analysis of the caloric test, first much exaggerated vertigo and falling, and second, absence of nystagmus from the right verticals. Pointing tests were impossible.

This indicates the supreme test in the ability to interpret a Bárány syndrome. The marked vertigo and falling suggest a lesion above the stem, but in this case the stem itself gave an abnormal response. The explanation is clear and in accordance with facts.

The most striking effects of supratentorial tumors or, in fact, of any brain tumor, are those of pressure. This we know may cause symptoms due to injury to remote parts of the brain, for example, a lesion above the stem may, due to its pressure, cause a paralysis or paresis of the sixth cranial nerve, resulting in a paralysis or paresis of the external rectus muscle of the eye. Similarly an enlargement of the sella tursica or an absence of the posterior clinoid process is shown by the roentgenogram. These two facts have been proved definitely in a large number of cases. The pressure in this case exerted not only a rather typical exaggeration of vertigo and falling, but also the effect of the pressure from above downward, resulting in a brain stem syndrome partially involving the posterior longitudinal bundles. From the Bárány, therefore, a diagnosis was made of a supratentorial tumor in the left cerebral hemisphere.

At operation Feb. 8, 1919, a subcortical tumor was found in the left frontal lobe, 2.5 cm. below the surface of the cortex, involving the middle and lower frontal convolutions.

Case A293010, Mr. A. St. L., aged 48, came to the Clinic Oct. 13, 1919, because of fits which began eighteen months before. The condition affected the right foot and arm and the head, occasionally the left side. Sometimes the attacks were followed by unconsciousness. The attacks were tonic in nature, started from the foot on the right side and passed up the same side, the head turning to the right. The fits lasted about ten minutes. The attacks were often preceded by an electric shock throughout the body. Formerly they occurred about every three weeks, at the time of examination once in seven weeks. The patient had severe frontal and occipital headaches, often lasting three days, and he complained of diplopia and tinnitus. He did not bite his tongue or froth at the mouth. He was rather dull intellectually and slow to answer questions. Sixteen years before in an explosion of dynamite a board had struck him in the left occipital region, but this had not appeared to give him any trouble.

Physical examination.—The patient's pupillary reflexes were sluggish. His body was erupted with marked pigmentation. He had a bilateral choked disc of two diopters in the right eye and of one diopter in the left. The routine examinations showed the blood and urine to be normal. The blood and spinal fluid Wassermann tests were negative to 0.4 c.c. of fluid. The Nonne was positive; there were five small lymphocytes.

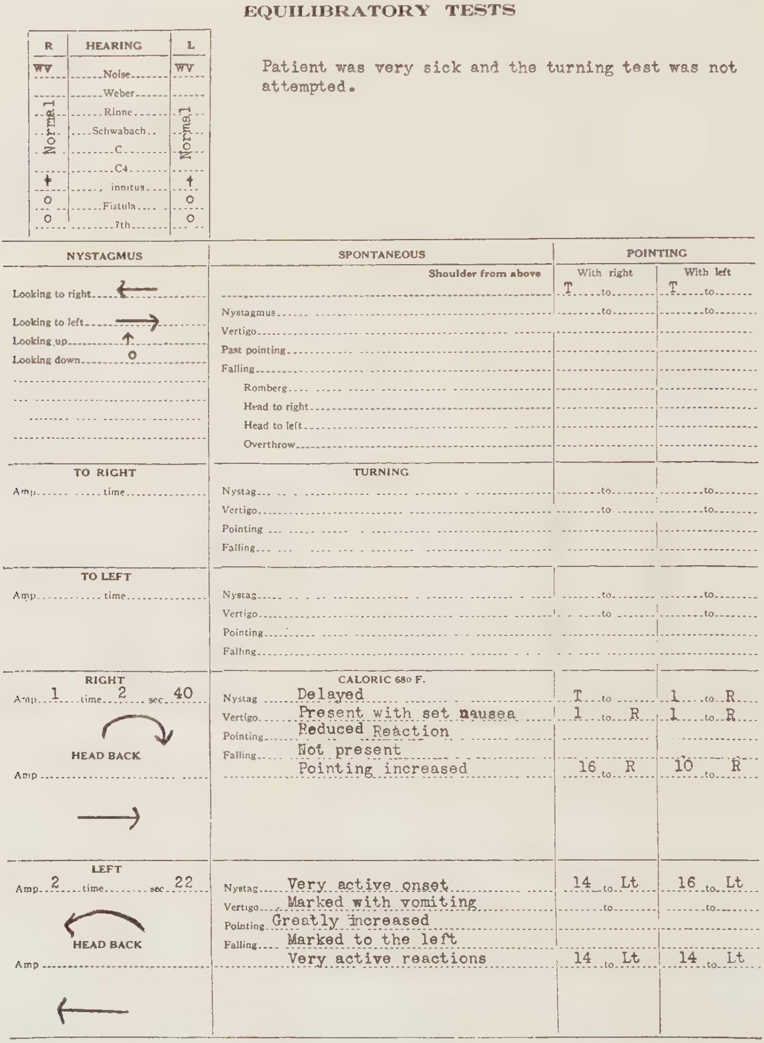
A roentgenogram of the head failed to reveal the sella, but a suspicious area of erosion was found in the occipital region. The patient's temperature was normal.

Neurologic examination (Jan. 31, 1920).—The patient was found to have normal vision, choked discs of two diopters on the left and one on the right, the right pupil slightly larger than the left, and a slight diminution in all the pupillary reflexes. Examination of the other cranial nerves was negative. Weakness was general, but there was not any evidence of local impairment in muscular power. Coordination was moderately impaired on the right side in both the arm and the leg, and very slightly impaired on the left. The gait suggested an ataxia and the Romberg test was slightly positive. Sensation, including sterognosis, was normal. On rest and on static innervation a coarse rapid tremor appeared in the right arm. The tendon reflexes were all moderately increased but equal on both sides. The abdominal and plantar reflexes were normal. The sphincter control was normal. Spinal fluid examination gave a negative Wassermann test, a positive Nonne, and five small lymphocytes to the cubic millimeter. The patient was strikingly sluggish mentally and indifferent in his cooperation during the examination. A roentgenogram of the head showed the outlines of the sella to be very indistinct.

A diagnosis of a brain tumor, probably of the left frontal lobe, was made, and exploration advised.

Bárány test.—The Bárány test was very interesting. The turning was not done because the patient was quite sick. The caloric test showed that the nystagmus time from the right vertical canals was markedly delayed. Vertigo was normal. There was no falling, and the pointing was reduced. The right horizontal canal showed increased pointing. Obviously, the turning was not necessary in this case, and a diagnosis was made of a left supratentorial tumor which was producing pressure signs on the right hemisphere (Chart 3).

The patient was operated on Nov. 27, 1919, and a large osteoplastic flap was turned on the left temporal area. Profuse bleeding was encountered, the dura near the mid line bleeding freely. The ventricle was entered twice with a trocar, but only a few drops of fluid escaped. In making the stabs it felt as if there was a tumor under this area of the dura; the dura was incised and a tumor measuring 7 cm. by 6 cm. was found, very closely adherent to the dura but encapsulated on the brain side. Enucleation was difficult and bloody, a large portion of the dura, about 4 cm. in diameter, was excised attached to the tumor (Figs. 169 and 170) which extended up to the mid line and



EQUILIBRATORY TESTS

R	HEARING	L
WV	Noise	WV
	Weber	
Normal	Rinne	Normal
	Schwabach	
	C	
	C4	
+	innitus	+
O	Fistula	O
O	7th	O

Patient was very sick and the turning test was not attempted.

NYSTAGMUS

Looking to right ← 2
Looking to left →
Looking up ↑
Looking down o

SPONTANEOUS	POINTING With right	POINTING With left
Shoulder from above	T to	T to
Nystagmus	to	to
Vertigo		
Past pointing		
Falling		
Romberg		
Head to right		
Head to left		
Overthrow		

TO RIGHT

Amp. time

TURNING		
Nystag	to	to
Vertigo	to	to
Pointing		
Falling		

TO LEFT

Amp. time

Nystag	to	to
Vertigo	to	to
Pointing		
Falling		

RIGHT

Amp. 1 time 2 sec. 40

HEAD BACK

Amp →

CALORIC 68° F.		
Nystag Delayed	T to	1 to R
Vertigo Present with set nausea	1 to R	1 to R
Pointing Reduced Reaction		
Falling Not present		
Pointing increased	16 to R	10 to R

LEFT

Amp. 2 time sec. 22

HEAD BACK

Amp ←

Nystag Very active onset	14 to Lt	16 to Lt
Vertigo Marked with vomiting	to	to
Pointing Greatly increased		
Falling Marked to the left		
Very active reactions	14 to Lt	14 to Lt

CHART 3. Case A293010.

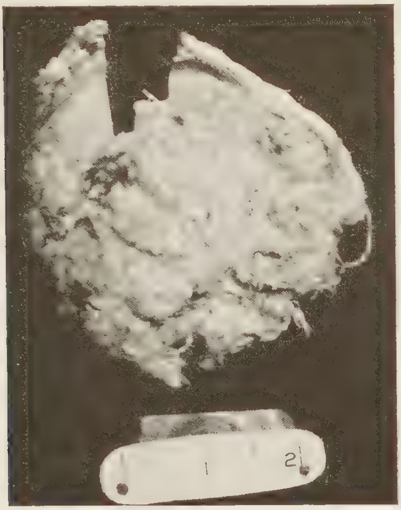


FIG. 169 (Case A293010).—Endothelioma of brain adherent to dura.

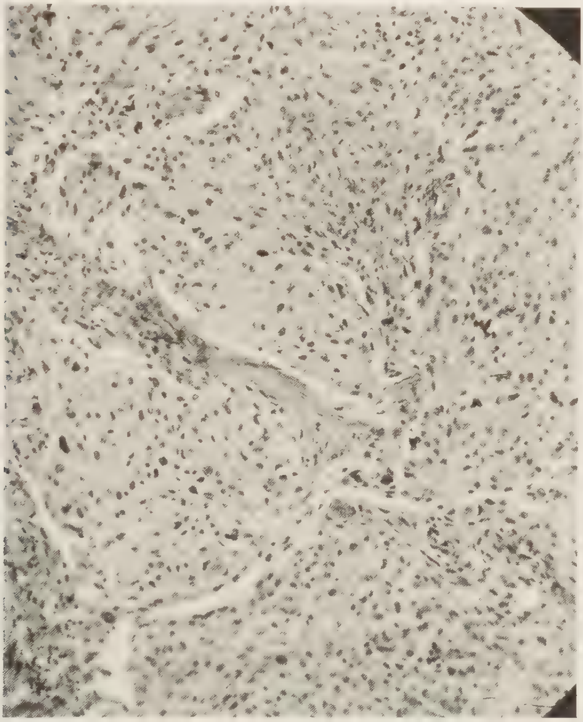


FIG. 170. (Case A293010).—Photomicrograph of section of gross specimen of endothelioma of brain shown in Figure 169. ×100.

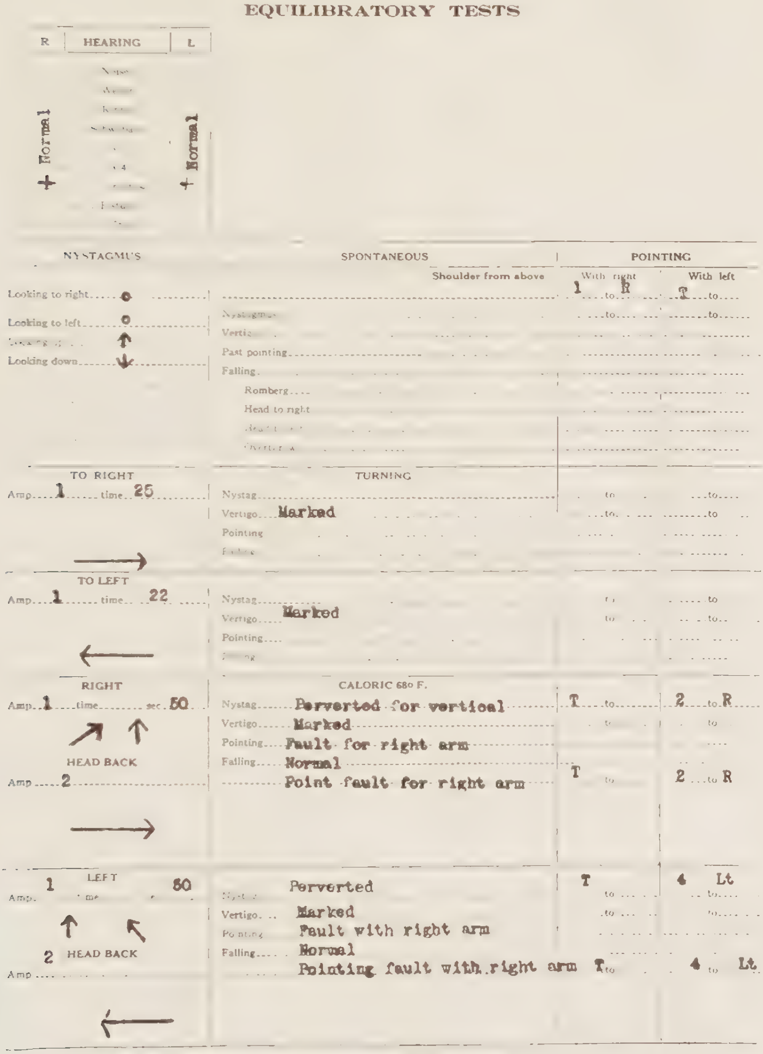
made pressure on the fax cerebri. The longitudinal sinus was probably entered as there were marked venous hemorrhages which required packing. The excavation in the brain was filled with animal membrane held in place by a silk suture. The operator noted that a cerebral hernia would develop due to the dural defect.

The patient recovered and had a resection of the small cerebral hernia. The tumor, 6 cm. in diameter, on pathologic examination was shown to be endothelioma.

The findings in this case were definite and instructive. The exact localization of the lesion was made from the caloric test alone. The pressure signs on the left hemisphere were verified by the location of the tumor. The patient had no convulsions after operation and feels considerably stronger.

Case A241430. Mr. H. H. W. H., aged 31, came to the Clinic Aug. 7, 1917, with a history of the onset of headaches in August, 1916, and shortly thereafter numbness of the left foot which gradually extended upward. He fell and a convulsion followed. His left leg and arm were cramped badly. He bit his tongue and frothed at the mouth. These spells occurred during the day and lasted about fifteen minutes. The symptoms were always the same and the attacks became more frequent, sometimes coming every day. The patient's grandmother was insane and his father a chronic alcoholic. The patient did not take stimulants. His mother and one brother were subject to severe sick headaches. He had two healthy children. He had had neisserian infections at the age of fourteen, sixteen, and twenty-three. Since Dec. 2, 1917, the patient had not worked because he felt too weak and had the spells almost daily. There was a tinnitus in his right ear. He had taken bromids for the past few weeks and had not had an attack.

Physical examination.—The patient was well nourished, weighed 132 pounds, and was 5 feet 6 inches tall. His speech was a little slow; the Romberg was positive. He had bilateral sensitive areas in both lower abdominal quadrants. His movements were a little unsteady and he responded slowly. His fundi were normal. The routine examinations of urine and blood, and the blood pressure tests were all normal. A test meal showed free hydrochloric acid of 68 and combined acid of 14. The blood Wassermann test and the spinal fluid Wassermann test in dilutions of 0.2, 0.3, 0.4, and 0.5 c.c. were negative. There was one small lymphocyte, and the Nonne was negative. The roentgenogram of the stomach was negative. A roentgenogram of the head showed a calcified area in the right parietal area. The temperature was normal.



EQUILIBRATORY TESTS

R | HEARING | L
+ Normal
+ Normal

NYSTAGMUS
Looking to right ○
Looking to left ○
↑
Looking down ↓

SPONTANEOUS
Past pointing
Falling
Romberg
Head to right

POINTING
Shoulder from above
With right: 1 to R
With left: T to

TO RIGHT
Amp 1 time 25

TURNING
Nystag
Vertigo Marked
Pointing

TO LEFT
Amp 1 time 22
Nystag
Vertigo Marked
Pointing

CALORIC 68° F.

RIGHT
Amp 1 sec. 50
Nystag Perverted for vertical — T to — 2 to R
Vertigo Marked
Pointing Fault for right arm
Falling Normal
HEAD BACK
Amp 2 — Point fault for right arm — T to — 2 to R

LEFT
Amp 1 50
Perverted — T — 4 Lt
Vertigo Marked
Pointing Fault with right arm
Falling Normal
2 HEAD BACK
Amp — Pointing fault with right arm — T to — 4 to Lt.

CHART 4. Case A241430.

Neurologic examination (Aug. 7, 1918).—The neurologic examination was negative with the exception of nystagmus. There were a very slight diminution in tactile sensibility over the left foot, a marked decrease in joint sensibility of the left toes, a very definitely increased tendoachillis reflex on the left, and bilateral absence of the abdominal reflexes. A roentgenogram of the head showed a calcified area in the right parietal region. The spinal fluid examinations were negative.

A diagnosis of migraine and Jacksonian epilepsy, due to a cortical lesion involving the foot center of the left rolandic area, was made and exploration advised.

Bárány test.—A Bárány test was made and showed a spontaneous vertical nystagmus with the patient looking up and a nystagmus down on looking downward (Chart 4). A spontaneous pointing fault was present with the left arm. The turning revealed an exaggeration of vertigo. The caloric test presented a perverted nystagmus on stimulation of the right and left vertical canals. Also all verticals gave marked vertigo and a pointing fault for the right arm. The horizontal canals showed a pointing fault with the right arm. The perverted nystagmus obtained in this case was due to an interference in the posterior longitudinal bundles. This, like almost all similar reactions, shows a partial loss of function rather than a total absence, which is typical of the responses due to pressure. There was also a pointing fault for the right arm from all canals. At first glance, this would seem to indicate a cerebellar lesion, because the synergetic movements are controlled by this part of the brain. Such an assumption was wrong in this case for two reasons; first because the pointing fault was only with the right arm, and second because stimuli do get through and produce normal past-pointing. This fault, therefore, is not due to a cerebellar lesion, but to an interference with the tracts leading to the hind-brain. Such an interference is explained by the effect of pressure on the middle cerebellar peduncles.

In this case the reaction consisted of exaggerated vertigo throughout all tests, perverted nystagmus from all vertical canals and a pointing fault for the right arm from all the semicircular canals. A Bárány diagnosis was therefore made of a supratentorial lesion causing considerable pressure downward on the peduncles, stem, and posterior longitudinal bundles. It was impossible to designate the side.

August 22, 1918, a large right subtemporal decompression was made. The cortex was opened and a diffuse, firm tumor was found in the sensory area of the right hemisphere. It was not encapsulated. As it could not be removed 50 mg. of radium were inserted. The tumor was firm and contained calcium.

Case A221019. Mr. J. A. M., aged 46, came to the clinic Feb. 5, 1918. He had been rather nervous, especially during the past two years. He slept well. He used no stimulant except tea once a day. He had one healthy child, aged 17. When the patient was 23 he was injured in a railroad wreck, receiving three wounds on his head. He was unconscious for three hours and was in bed for three or four weeks. November 7, 1916, a tumor had been removed from the back of his right thigh. The tumor was not examined pathologically nor preserved. December 9, 1917, a second operation was performed in the scar of the former operation, the details of which are uncertain, and a rectal operation performed for epilepsy.

The patient's clinical history centered around his epileptic spells. The first attack occurred Oct. 21, 1917, the first premonition being temporary blindness, followed by twitching of the eyes. The patient cried out and fell over unconscious in a generalized convulsion accompanied by vomiting and frothing at the mouth. He was unconscious for one and one-half hours and awoke very tired and nervous. He had had about fifteen attacks in the last three months; the last one was ten days before examination. The attacks had become more frequent but less severe. The patient complained of gastric symptoms with belching of gas. About Jan. 1, 1918, he had severe colic and upper abdominal pain with vomiting for one and one-half hours. His bowels were regular and his appetitie good. He had had almost constant, severe headaches in the back of his head and behind the right ear, but frequently diffuse and bilateral since the onset of trouble. His vision was faulty, and he often found it difficult to touch his nose with his finger.

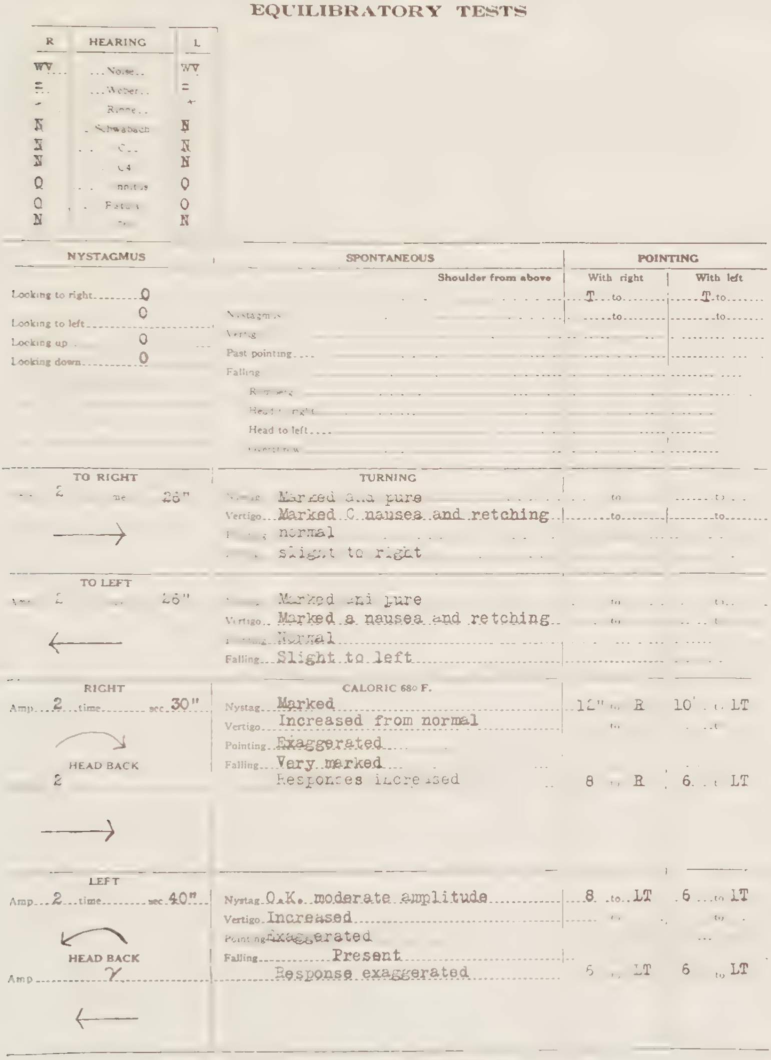
Physical examination. The patient walked to the clinic unaided. He was 5 feet and 9 inches tall and weighed 171 pounds; four months before he had weighed 200 pounds. There was a scar on his right thigh posteriorly with no signs of recurrence of the former tumor, which probably was a fatty tumor. The rectal and abdominal examination was negative. He had a definite pyorrhea alveolaris. The systolic blood pressure was 108, and the diastolic 76. A twelve-hour specimen of 350 c.c. of urine was acid in reaction and showed a specific gravity of 1021. All other macroscopic and microscopic tests were normal. Hemoglobin was 70 per cent. The red blood count was 4,448,000 and the white 9,400. The blood Wassermann test and the spinal fluid test in dilutions of 0.2, 0.3, 0.4, and 0.5 c.c., using Noguchi and Melange antigen, were negative. There were seven small lymphocytes in the spinal fluid. The Nonne test was negative. The blood cholesterol estimated in milligrams for 100 c.c. by the Bloor I method was 0.400, and by the Bloor II method 0.444, a difference of 0.044. Roentgenograms of the head and chest were also negative. The temperature was 98.6. Examinations of the ear, nose, nasopharynx, throat, larynx, and auditory acuity were normal.

Neurologic examination (Feb. 5, 1918).—Both pupils were somewhat irregular. A slight nystagmus was noted. Vision was normal in both eyes, the fields showed no contraction, and the fundi did not reveal any evidence of pressure. The cranial nerves showed no abnormality except that on smiling the patient wrinkled the left side of the face somewhat more than the right. The grip on the left, as tested with the dynamometer, registered 20, and on the right, 26. The power of the other muscles of the left arm and left leg was likewise very slightly less than that of the right. The tendon reflexes were somewhat more active on the left than on the right. The plantar response was flexor on both sides. Sensation was normal throughout. Coördination was normal on the right, but slightly impaired on the left. There was a very slight static tremor in the hands. Speech was slurring. The patient was considerably demented so that coöperation was unsatisfactory. His handwriting showed no changes of significance. The spinal fluid reactions were normal.

The diagnosis was uncertain; however, exploration of the right motor area of the brain for tumor seemed justified.

Bárány test.—The Bárány test (Chart 5) showed no spontaneous pointing faults, normal hearing, and no spontaneous nystagmus. The turning tests were normal except that the vertigo was unusually marked and accompanied by much nausea and retching. The caloric test revealed a rotatory nystagmus to the left of moderate amplitude on stimulation of the right vertical canals in thirty seconds. The pointing and falling tests were increased over normal. The responses from the right horizontal canal were increased, following the onset of a horizontal nystagmus to the left. On stimulation of the left vertical canals there was a rotatory nystagmus to the right of moderate amplitude in forty seconds. All tests and responses from these canals were exaggerated. Stimulation of the left horizontal canal produced a horizontal nystagmus to the left of moderate amplitude with the accompanying responses exaggerated.

The Bárány test in this case is characterized by a generalized exaggeration of all responses without any reactions being absent or diminished. A diagnosis, from the Bárány test, of a supratentorial lesion was made. It was impossible in this case to name the hemisphere. After a consultation with the neurologists, a final diagnosis of a tumor of the brain in the right motor area was made and exploration advised.



EQUILIBRATORY TESTS

R	HEARING	L
WV	Noise	WV
=	Weber	=
-	Rinne	+
N	Schwabach	N
N	C	N
N	C4	N
O	Tinnitus	O
O	Fistula	O
N		N

NYSTAGMUS

Looking to right O
Looking to left O
Looking up O
Looking down O

SPONTANEOUS — Shoulder from above

POINTING — With right: T to — With left: T to

Nystagmus
Vertigo
Past pointing
Falling
Head to left

TO RIGHT — 2 — time 26"

TURNING

Nystag. Marked and pure
Vertigo. Marked c nausea and retching
Pointing normal
Falling slight to right

TO LEFT — Amp. 2 — 26"

Nystag. Marked and pure
Vertigo. Marked c nausea and retching
Pointing Normal
Falling. Slight to left

RIGHT — Amp. 2 time sec. 30"

CALORIC 68° F.

Nystag. Marked — 12" to R — 10' to LT
Vertigo. Increased from normal
Pointing. Exaggerated
Falling. Very marked

HEAD BACK — 2

Responses increased — 8 to R — 6 to LT

LEFT — Amp. 2 time sec. 40"

Nystag. O.K. moderate amplitude — 8 to LT — 6 to LT
Vertigo. Increased
Pointing. Exaggerated
Falling. Present

HEAD BACK — Amp. ϒ

Response exaggerated — 5 to LT — 6 to LT

CHART 5. Case A221019.

At operation, Feb. 25, 1918, a nodular and moderately vascular tumor about 6 cm. in diameter was removed by blunt dissection from the right frontomotor area.

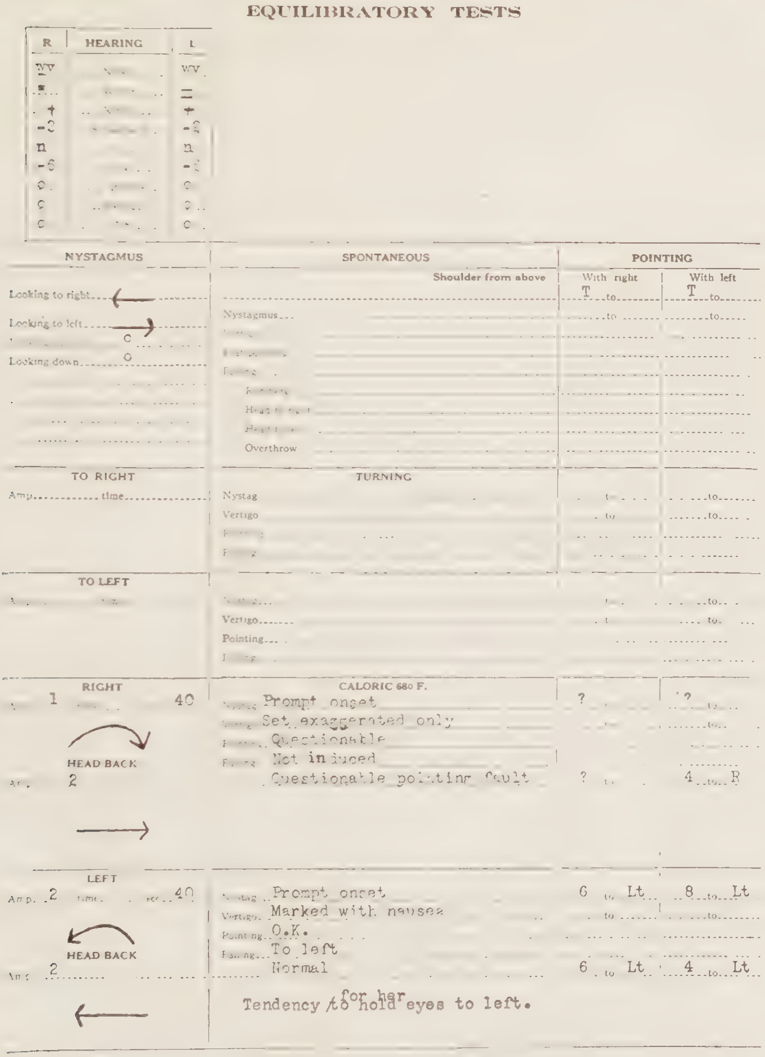
Case A246431. Miss D. D., aged 17, came to the clinic Sept. 21, 1918, complaining chiefly of blindness and headaches. The patient entered the clinic walking, but directed by her father. Her grandfather and aunt on her mother's side died of tuberculosis; one aunt died of cancer. The grandmother and two sisters on the father's side died of tuberculosis. The patient since nursing at the breast had had attacks simulating petit mal, typhoid fever at six years of age, malaria in 1917, and repeated rheumatic attacks. Her menses began at twelve and were painful. In February, 1918, she had attacks of pain in the eyes and noticed that her vision was getting poor. Photophobia was marked. The patient often vomited when the headaches were severe, but the vomiting was not of the projectile type. She was relieved of this by lying down and closing her eyes. Sight began rapidly to disappear and was gone in ten days. It disappeared first in the right eye, which had pained her most. At the time of examination she could see only bright lights at night and petit mal attacks were occurring two or three times daily.

Physical examination.—The patient, whose family is inclined to obesity, weighed 227 pounds and was 5 feet and 6 inches in height. The examination revealed few abnormalities. Her entire abdomen was tender to touch. There was doubtful light perception in the right eye. The discs had swollen margins with complete secondary atrophy of the nerve heads. The vitreous contained many small stringy floating opacities from a low grade uveitis. The blood Wassermann tests in dilutions of 0.3 and 0.4 c.c. were negative. The vaginal smear showed gonococci. There was a trace of albuminuria. The white blood cell count was 14,000. The other routine tests were normal. A roentgenogram of the head showed a calcified area in the right temporal region with evidence of intracranial pressure.

Neurologic examination (Sept. 21, 1918).—On neurologic examination a complete blindness from secondary optic atrophy, with a divergent strabismus, was noted. The pupils were dilated and did not respond to light. The patellar reflexes could be obtained only on reinforcement, and the tendo-Achilles responses were considerably diminished. The plantar reflexes were uncertain, but probably flexor.

A diagnosis of probable brain tumor, without definite localizing signs, was made.

Bárány test.—In carrying out the Bárány test (Chart 6) turning was not done because of the patient's physical condition. There was spontaneous bilateral horizontal nystagmus. The hearing test showed the high fork and the Schwabach test slightly reduced. The pointing was normal. In analyzing the caloric test we noted a prompt response in the nystagmus from all vertical canals. Vertigo was



EQUILIBRATORY TESTS

R	HEARING	L
WV		WV
=		=
+		+
-2		-2
n		n
-6		-2
0		0
0		0
0		0

NYSTAGMUS
Looking to right ←
Looking to left →
0
Looking down 0

SPONTANEOUS
Shoulder from above
Nystagmus
Overthrow

POINTING
With right T to
With left T to

TO RIGHT
Amp. time

TURNING
Nystag
Vertigo

TO LEFT
Vertigo
Pointing

RIGHT
1 40
HEAD BACK
2
→

CALORIC 68° F.
Prompt onset ? ?
Set exaggerated only
Questionable
Not induced
Questionable pointing fault ? 4 to R

LEFT
Amp. 2 time 40
Nystag. Prompt onset 6 to Lt 8 to Lt
Vertigo Marked with nausea
Pointing O.K.
Falling To left
HEAD BACK
Amp. 2 Normal 6 to Lt 4 to Lt
←

Tendency ~~to~~ for her to hold eyes to left.

CHART 6. Case A246431.

exaggerated in both instances, but much more on the left side than on the right. The pointing tests were questionable chiefly because the patient complained of vertigo and her coöperation was poor. However, a response with the left hand came through on stimulation of the right horizontal canal and a lesion of the cerebellum was thereby eliminated. When the left canals were tested there was a tendency to hold the eyes to the left. The right cerebellum was considered normal, because a normal reaction was obtained. The Bárány test showed, therefore, prompt nystagmus associated with exaggerated vertigo, falling, conjugate deviation of the eyes, and pointing faults, and the diagnosis therefrom was supratentorial tumor causing pressure on the stem and middle cerebellar peduncles.

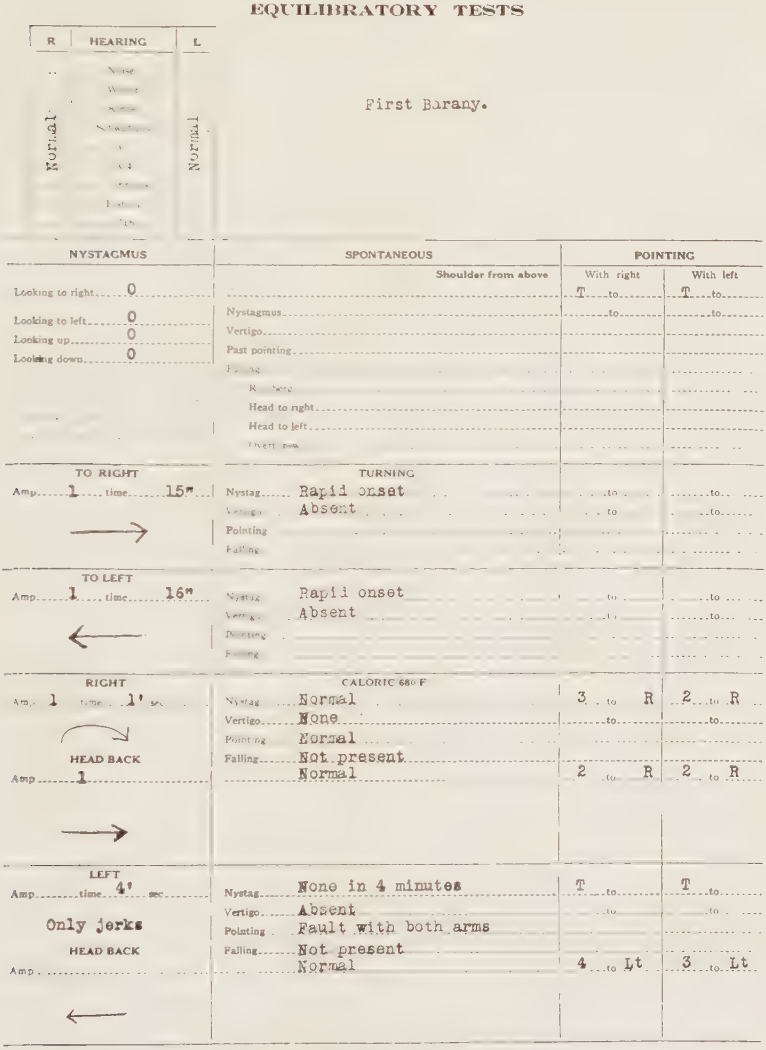
November 1, 1918, a large subtemporal decompression was performed on the right side. Two and one-half centimeters below the surface a mass was found in the right cerebral hemisphere which contained yellow mucilaginous fluid. The tumor was not encapsulated and hence enucleation was not attempted. The patient recovered from the operation and went home.

Case A224782. E. S., a girl aged 7, was brought to the Clinic March 11, 1918. The child had had a bilateral frontal headache August, 1917, and had appeared dazed for ten minutes. After two months the headaches were more frequent and severe, and accompanied by projectile vomiting. The patient walked into the clinic without aid. She was the second child of a large family. She had had scarlatina at 3, pertussis at 5, measles and chicken-pox at 7. A choked disc had been diagnosed in December, 1917.

Physical examination.—The physical findings and laboratory tests were negative. The temperature was normal. Blood Wassermann tests on the child and parents were negative. The von Pirquet test was normal. A roentgenogram of the head did not aid in the diagnosis.

Neurologic examination (March 11, 1918).—The neurologic examination showed the pupils to be moderately dilated; reaction to light was normal on the left, but on the right was followed by a secondary dilatation; vision in the right was 20/200 and in the left was reduced to the counting of fingers. There were bilateral choked discs. The mental condition was normal. Otherwise the findings were negative throughout. July 15, 1918, the patient had developed a marked nystagmus, described in detail on the Bárány sheet.

Bárány test.—The Bárány test (Chart 7) revealed active nystagmus on turning, with absence of vertigo. The caloric test of the right canals showed an absence of vertigo and falling. On the left, however, an absence of nystagmus was obtained from the vertical canals accompanied by the absence of vertigo and falling. There was also a pointing fault for both arms. The right horizontal tract responded in



EQUILIBRATORY TESTS

R	HEARING	L
Normal		Normal

First Barany.

NYSTAGMUS	SPONTANEOUS	POINTING	
	Shoulder from above	With right	With left
Looking to right 0		T to	T to
Looking to left 0	Nystagmus	to	to
Looking up 0	Vertigo		
Looking down 0	Past pointing		
	Falling		
	Romberg		
	Head to right		
	Head to left		
	[illegible]		
TO RIGHT	TURNING		
Amp 1 time 15"	Nystag Rapid onset	to	to
→	Vertigo Absent	to	to
	Pointing		
	Falling		
TO LEFT			
Amp 1 time 16"	Nystag Rapid onset	to	to
←	Vertigo Absent	to	to
	Pointing		
	Falling		
RIGHT	CALORIC 68° F		
Amp 1 time 1' sec	Nystag Normal	3 to R	2 to R
↷	Vertigo None	to	to
HEAD BACK	Pointing Normal		
	Falling Not present		
Amp 1	Normal	2 to R	2 to R
→			
LEFT			
Amp time 4' sec	Nystag None in 4 minutes	T to	T to
	Vertigo Absent	to	to
Only jerks	Pointing Fault with both arms		
HEAD BACK	Falling Not present		
Amp	Normal	4 to Lt	3 to Lt
←			

CHART 7. Case A224782.

a normal manner. A diagnosis was made of pressure from above, on the mid-stem region especially on the left, accompanied by a disturbance in the cerebellar tracts in the middle cerebellar peduncle on the left. A summary of the entire case revealed the pressure of an intracranial lesion without localizing signs. On account of the few findings it was decided to do a lumbar puncture every three to five days, withdrawing 8 to 15 c.c. of fluid, and within a few hours to examine the fundi. This therapy had little effect and the choked discs did not change.

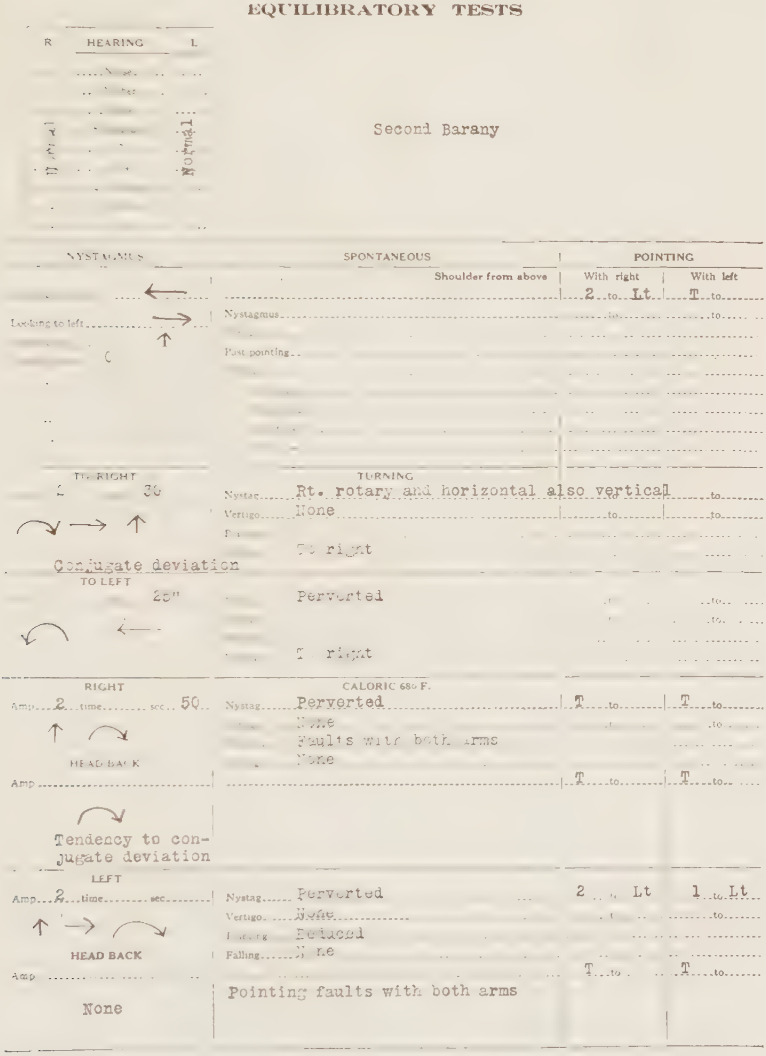
A right subtemporal decompression and exploration was done April 1, 1918; no tumor was found. The patient left the clinic but did not improve.

September 19, 1918, the patient returned. At this time she inclined toward the left in walking or sitting. She had involuntaries on awakening in the morning and on rising had a tendency to fall backward. She had tinnitus in the right ear. No loss of motion was noted, but she felt "dopey" all that day.

Neurologic examination (Sept. 19, 1918).—The optic atrophy and loss of vision were complete. The pupils were dilated and reacted only to accommodation. Marked nystagmus was still present. Speed of voluntary movements was moderately reduced over the entire right side, although the coördination tests were practically normal. A tremor of moderate rate and small amplitude developed on movement. The plantar reflex by the Babinski method was extensive on the right and doubtful on the left. At times, particularly in the morning, there was a tendency to urinary incontinence. Percussion of the head did not reveal local tenderness and imparted a cracked-pot resonance. No other significant abnormalities were noted.

A diagnosis of brain tumor was made; however, localization was by no means certain. The signs suggested a cerebellar involvement.

Bárány test.—A second Bárány test (Chart 8) was made which presented very definite changes from the first. There was now a spontaneous bilateral horizontal nystagmus and vertical nystagmus on looking up. A spontaneous pointing fault with the left arm was also found. The right canals, on turning, gave a perverted nystagmus composed of a rotatory and horizontal nystagmus accompanied by a vertical nystagmus. There was also conjugate deviation of the eyes and falling to the right, without subjective vertigo. By stimulating the right vertical canals with cold water, a perverted nystagmus occurred in fifty seconds, consisting of a vertical and a left rotatory nystagmus. The stimulation of the horizontal canals produced a rotatory nystagmus to the left and conjugate deviation. There were also pointing faults with both hands. When the left verticals were similarly stimulated a perverted nystagmus began almost at once, consisting of a vertical, horizontal, and rotatory nystagmus to the left.



EQUILIBRATORY TESTS

R HEARING L

Normal Normal

Second Barany

NYSTAGMUS

Looking to left

SPONTANEOUS

Shoulder from above

Nystagmus

Past pointing

POINTING

With right 2 to Lt

With left T to

TO RIGHT

2 30

Conjugate deviation

TURNING

Nystag. Rt. rotary and horizontal also vertical

Vertigo None

To right

TO LEFT

25"

Perverted

To right

RIGHT

Amp. 2 time sec. 50

HEAD BACK

Amp

Tendency to conjugate deviation

CALORIC 68° F.

Nystag. Perverted T to T to

None

Faults with both arms

None

T to T to

LEFT

Amp. 2 time sec.

HEAD BACK

Amp

None

Nystag. Perverted 2 Lt 1 to Lt

Vertigo None

Reduced

Falling None

T to T to

Pointing faults with both arms

CHART 8. Case A224782.

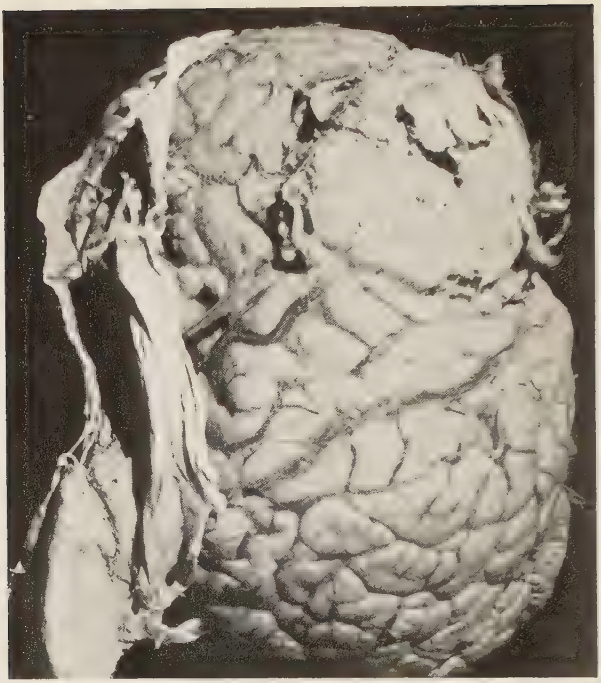


FIG. 171 (Case A224782).—Brain showing glioma of the right frontal lobe.

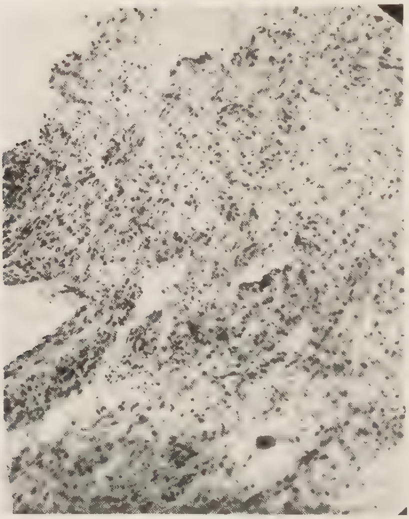


FIG. 172 (Case A224782).—Photomicrograph of glioma of right frontal lobe of brain shown in Figure 171.

There was no nystagmus found on stimulation of the horizontal canal. There was no subjective vertigo or falling. A pointing fault with both hands occurred when the horizontal canal was activated.

A diagnosis, from the Bárány test, of a lesion in the right cerebral hemisphere causing great pressure downward, was made.

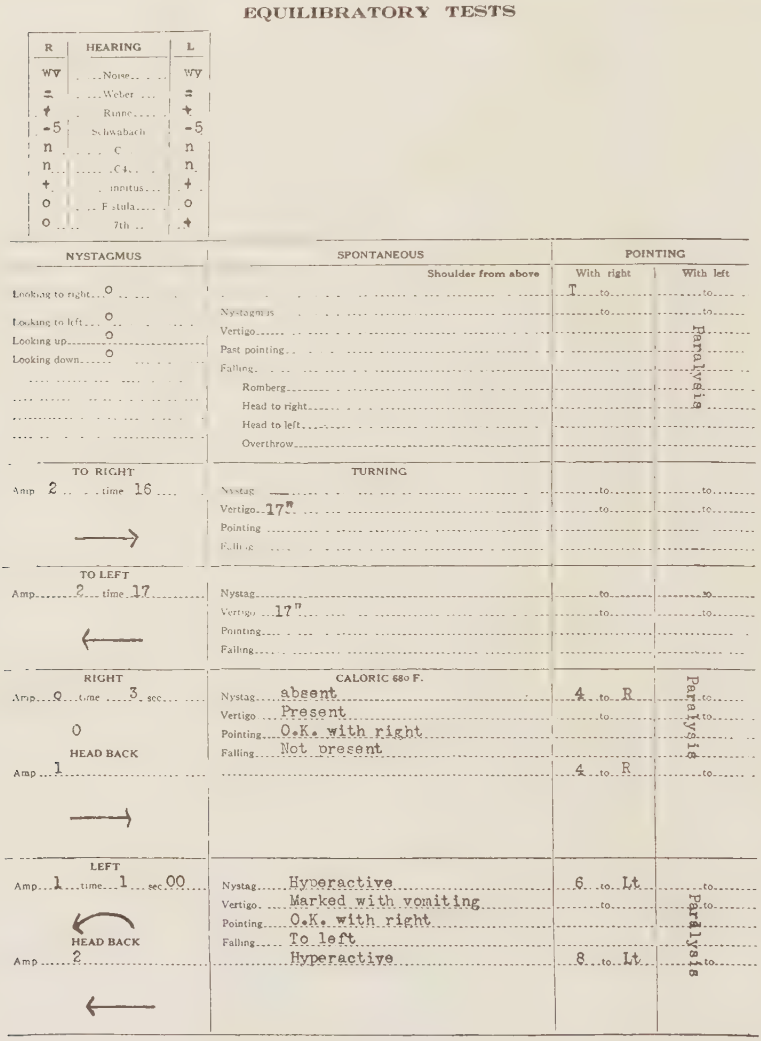
The second Bárány test shows very definitely the effect of prolonged and increased pressure on the stem, posterior longitudinal bundles, and on the middle cerebellar peduncles. The pressure was more intense on the right side as evidenced by the preverted nystagmus and conjugate deviation which occurred on the right side only. This effect was also evidenced by the fact that the middle cerebellar peduncle on the right was interfered with to the extent that stimuli did not get through to the cerebellum. Evidences of marked pressure signs appeared through both Bárány tests, especially the second.

After considerable deliberation a simple cerebellar decompression was performed Sept. 20, 1918. The exploration revealed nothing. The patient died Sept. 22, 1918, of a bilateral lobar pneumonia. Necropsy revealed a glioma of the right frontal lobe measuring 6 by 8 by 5 cm., just anterior to the explored area (Figs. 171 and 172).

Case A248887. Mr. E. B., aged 32, came to the clinic Oct. 16, 1918. The patient's health had been good until March, 1918, when he began to have severe occipital headaches often accompanied by vomiting, more marked on the right side. In April, 1918, weakness developed in the left arm and extended to the left leg. The weakness gradually increased until June, and the left side of the face became paralyzed. The patient had been a steady alcoholic until March, 1918. The family history was not important.

Physical examination.—The physical findings were negative. The blood pressure, urine, and blood were normal. The blood Wassermann test and the spinal fluid Wassermann test with 0.3 and 0.4 c.c. were negative. There was one lymphocyte. The Nonne was negative. There was no choked disc. The roentgenogram showed a very large Sella and apparently a calcified pineal body.

Neurologic examination. (Oct. 19, 1918).—Record was made of normal vision, an active bilateral neuroretinitis, a spontaneous nystagmus, a slight inequality in the size of the pupils, the left being somewhat larger than the right, and a pupillary reaction which was slow, but of good amplitude. Rotation of the eyeballs upward was limited. The muscles supplied by the middle and lower divisions of the left facial nerve were slightly but very definitely weak. The left arm and leg showed a moderate weakness with a corresponding diminution in speed and increase in tonus. Coördination in the left



EQUILIBRATORY TESTS

R	HEARING	L
wv	Noise	wy
=	Weber	=
+	Rinne	+
-5	Schwabach	-5
n	C	n
n	C4	n
+	Tinnitus	+
0	Fistula	0
0	7th	+

NYSTAGMUS
Looking to right 0
Looking to left 0
Looking up 0
Looking down 0

SPONTANEOUS — Shoulder from above — POINTING: With right T to; With left to
Nystagmus — to — to
Vertigo
Past pointing
Falling
Romberg
Head to right
Head to left
Overthrow
With left: Paralysis

TO RIGHT
Amp 2 time 16

TURNING
Nystag —— to to
Vertigo 17" to to
Pointing
Falling

TO LEFT
Amp 2 time 17
Nystag to to
Vertigo 17" to to
Pointing
Falling

RIGHT
Amp 0 time 3 sec
0
HEAD BACK
Amp 1

CALORIC 68° F.
Nystag absent — 4 to R — to
Vertigo Present — to — to
Pointing O.K. with right
Falling Not present
— 4 to R — to
With left: Paralysis

LEFT
Amp 1 time 1 sec 00
HEAD BACK
Amp 2

Nystag Hyperactive — 6 to Lt — to
Vertigo Marked with vomiting — to — to
Pointing O.K. with right
Falling To left
Hyperactive — 8 to Lt — to
With left: Paralysis

CHART 9. Case A248887.

arm was somewhat impaired. The thigh-trunk sign of Babinski was positive on the left. The gait was that of a patient with a left-sided hemiplagia. Touch and pain sensibilities were slightly diminished over the entire left side and moderately active on the right; the abdominal reflexes on the left were absent and on the right diminished; the plantar responses were normal. Attention and coöperation were very poor. The spinal fluid findings were negative.

The neurologic diagnosis was tumor cerebri of the right frontomotor area, probably subcortical and diffuse.

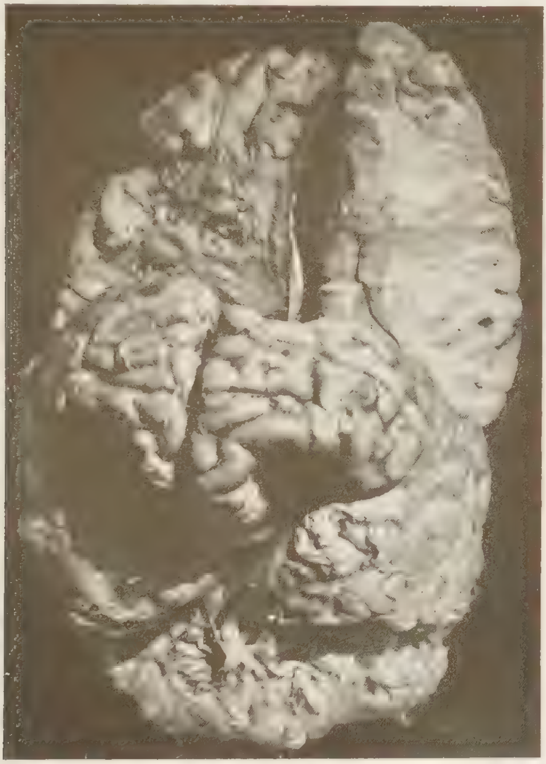


Fig. 173 (Case A248887).—Brain showing area from which smooth walled cyst was removed at operation.

Bárány test. A Bárány test (Chart 9) showed a generalized hyperactivity of responses throughout, except the nystagmus from the right verticals. On turning, the responses of nystagmus were of decreased duration. The caloric test showed an absence of nystagmus on stimulation of the right vertical canals for three minutes; this was accounted for on the basis of pressure from above. The effect of pressure from above explains the absence of falling and the slightly reduced vertigo.

The left vertical canals presented normal nystagmus time, but vertigo was markedly increased and associated with vomiting, thus giving evidence of exaggerated responses. Falling was to the left. Pointing was normal for all canals with the right arm, but absent with the left, due to the hemiplegia. Exaggerated responses, especially on the left, with pressure effect on the left brain stem were present. This, in the presence of a definite hemiplegia, made the diagnosis absolute. The Bárány report was the presence of a supratentorial lesion in the right cerebral hemisphere.

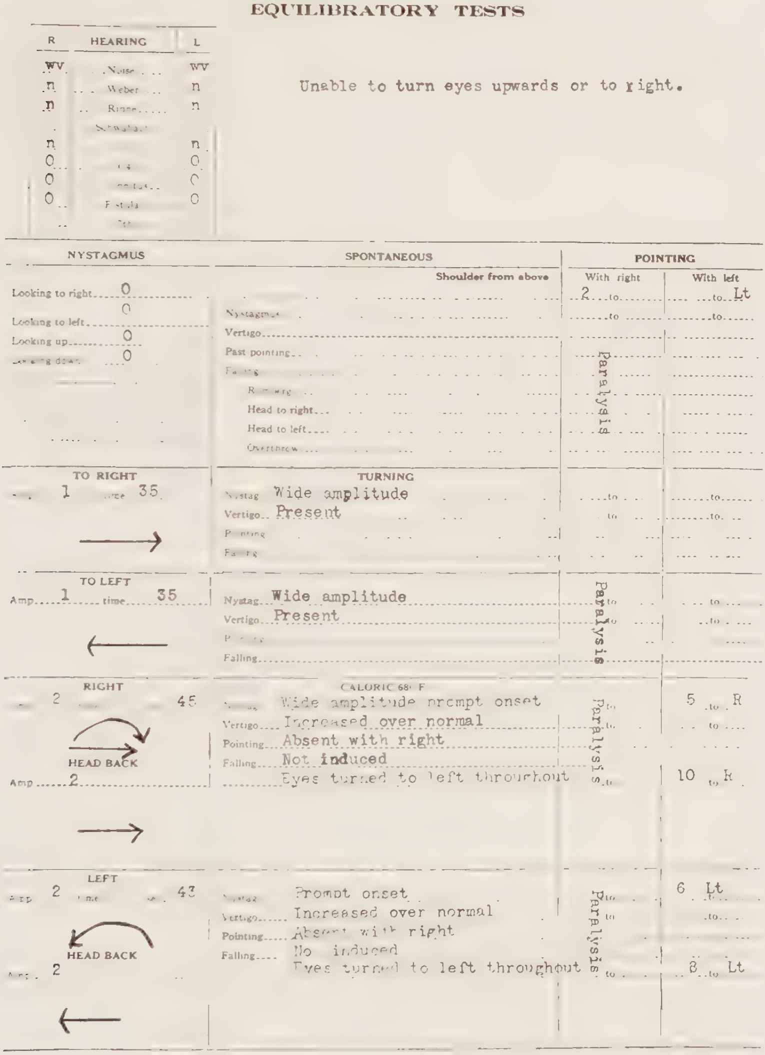
October 26, 1918, a cyst was removed from the right frontomotor area. The microscopic diagnosis showed the tissue to be that of a smooth-walled cyst (Fig. 173).

Case A308888. N. K., a boy aged 10, was admitted to the clinic March 16, 1920. The patient had been well until October, 1918, when he developed a headache, followed by right side convulsions which continued several hours until chloroform was given. Occasional spells of unconsciousness occurred every week or two. In March, 1919 a blood test was made and several salvarsan injections were given followed by iodids and bromids. The child was entirely free from trouble for two months in the fall of 1919. In December he again had attacks of headaches followed by unconsciousness. About six weeks before examination pain in the right leg developed which lasted several hours. In February, 1920, a definite weakness of the right arm and leg and a limp were noticed, and the convulsions became more frequent and severe, with twitching of the right side of the face. The child had been unable to walk for the past week. He had had two tonsil and adenoid operations.

Neurologic examination. (March 16, 1920).—Choked discs of three diopters on the left and of two diopters on the right, with normal vision, were disclosed. There was a slight ptosis on the left. Muscular movements of the forehead and about the mouth on the right were diminished in strength. There was a marked right-side hemiplegia. The tendon reflexes on the right were more active than those on the left; the superficial reflexes were normal. The patient had a very marked motor aphasia.

The neurologic diagnosis was tumor involving the left pre-central area.

Bárány test.—The Bárány test (Chart 10) revealed normal hearing and no spontaneous nystagmus. The caloric test of the right vertical canals showed a mixed type of rotatory and horizontal nystagmus to the left, of wide amplitude. Vertigo was exaggerated, as were the pointing tests for the left arm. The hemiplegia made all pointing tests with the left arm impossible. The right horizontal canal showed a horizontal nystagmus to the left of wide amplitude with exaggerated past-pointing with the left arm. The stimulation of the left vertical



EQUILIBRATORY TESTS

R	HEARING	L
WV	Noise	WV
n	Weber	n
n	Rinne	n
	Schwabach	
n		n
0	[illegible]	0
0	[illegible]	0
0	Fistula	0
	[illegible]	

Unable to turn eyes upwards or to right.

NYSTAGMUS	
Looking to right	0
Looking to left	0
Looking up	0
Looking down	0

SPONTANEOUS	POINTING With right	POINTING With left
Shoulder from above	2 to	to Lt
Nystagmus	to	to
Vertigo		
Past pointing	Paralysis	
Falling		
Romberg		
Head to right		
Head to left		
Overthrow		

TO RIGHT	TURNING	With right	With left
Amp 1 time 35	Nystag Wide amplitude	to	to
	Vertigo Present	to	to
→	Pointing		
	Falling		

TO LEFT	TURNING	With right	With left
Amp 1 time 35	Nystag Wide amplitude	Paralysis to	to
	Vertigo Present	to	to
←	Pointing		
	Falling		

RIGHT	CALORIC 68° F	With right	With left
Amp 2 time 45	Nystag Wide amplitude prompt onset	Paralysis to	5 to R
HEAD BACK	Vertigo Increased over normal	to	to
	Pointing Absent with right		
	Falling Not induced		
Amp 2	Eyes turned to left throughout	to	10 to R
→			

LEFT	CALORIC 68° F	With right	With left
Amp 2 time 43	Nystag Prompt onset	Paralysis to	6 to Lt
HEAD BACK	Vertigo Increased over normal	to	to
	Pointing Absent with right		
	Falling No induced		
Amp 2	Eyes turned to left throughout	to	8 to Lt
←			

CHART 10. Case A308888.

canals with cold water revealed a rotatory nystagmus to the right of wide amplitude, and of very prompt onset. Vertigo and past-pointing were exaggerated. Stimulation of the left horizontal canal revealed increased vertigo and past-pointing. The eyes remained turned to the left.

A Bárány diagnosis was made of a supratentorial tumor in the left hemisphere.

The patient was operated on March 15, 1920, and a large tumor measuring 5 by 4 by 3 cm. was partially removed from the surface of the left temporoparietal lobe, posterior to the fissure of Rolando. The tumor was not encapsulated and it was impossible to remove it entirely. The pathologist reported a glioma (Fig. 174).

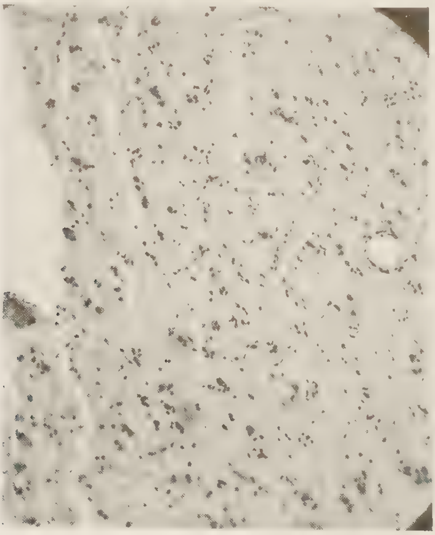


Fig. 174 (Case 308888).—Photomicrograph of glioma removed at operation from left temperoparietal lobe of the brain.

DISCUSSION

The nine cases of proved tumors above the tentorium, all of which were primarily and independently diagnosed by the Bárány test, present many interesting features.

In general, there are two large groups of phenomenon-syndromes that are typical of supratentorial tumors. The first group shows a very clear and marked response of nystagmus, vertigo, falling, and past-pointing. If the lesion is near the surface in one cerebral hemisphere, this reaction will be on the side of the lesion. Such unilateral activity of all responses cannot present any difficulty in the localization of the lesion. Symptoms of the second large group, while not so common, are just as typical of cerebral tumor as those of the first group, in which there is very clearly an active response of the nystagmus from one set of canals only, associated with an interference with the tracts in the stem or peduncles, and giving rise to diminished responses or to absence of the responses ordinarily attributed to these areas. In other words, the predominating feature, aside from an early and exaggerated nystagmus, may be the responses due to pressure.

It has been known for some time that the pressure of these tumors frequently present the only signs and symptoms of an intracranial lesion. Choked disc and enlargement of obliteration of the sella are two notable examples which have little to do with the location of a brain lesion, but which are due to the increased intracranial pressure. So too, the Bárány test may show an apparent predominance of responses ordinarily attributed to the stem or peduncles which yet, with an exaggerated nystagmus, are due to pressure. Furthermore, these pressure responses may be on the same side or on the opposite side of the lesion. With an exaggerated and early response of nystagmus a Bárány test may reveal only those responses ordinarily attributed to a fault in the cerebellum, yet this latter response is entirely due to the pressure effects on the tracts leading to the hind-brain. This effect of pressure may be so marked that a pointing fault may be obtained for both arms from all the canals on one side, but, as a rule, by prolonged stimulation it is possible in these cases to get a stimulation through and thus obtain normal past-pointing from one or both arms.

It is noteworthy that the Bárány test is frequently the only test or group of tests which localizes an intracranial lesion. While this is perfectly true, it is a colossal error for any one doing such tests to be independent of all other factors in the case. It is frequently of the highest value to consult with the neurologist after the Bárány diagnosis has been made.

There is another interesting observation, noted in my experience of more than fifty Bárány tests indicating supratentorial lesions, which may explain the absence or predominence of phenomenon-syndromes attributed to pressure associated with cerebral lesions in different areas. In lesions on or near the surface of the cerebrum the Bárány usually shows all responses exaggerated, with little or no pressure phenomena. On the other hand, lesions deep in the cortex usually show but slightly exaggerated responses, associated with marked reduction of other responses due to pressure. This observation, while very striking, is not conclusive. Many Bárány tests can be explained more easily by this theory than by any other. Some of the cases presented here exemplify this observation.

In order to make clear the relative position of the Bárány in the tumors localized in the cerebrum, it will only be necessary to state that the diagnosis of the location of an intracranial lesion by this test is considered as only one of a chain of evidences when the final diagnosis is determined by the neurologist. Hence, the final location of such a tumor is made by the neurologist, who considers all symptoms and signs including the Bárány test. The operative and necropsy findings should also be studied in checking up on Bárány responses which apparently do not fit, or which at least make the exact localization of a lesion difficult.

CONCLUSIONS

Conclusions drawn from nine proved cases of supratentorial tumors are not, of course, sufficient to account for the relation of the Bárány test to lesions above the stem. However, conclusions as follow may be made:

1. A phenomenon-syndrome consisting of exaggerated nystagmus, vertigo, falling, and past-pointing suggests a Bárány diagnosis of a supratentorial lesion.

2. The more typical reactions may be complicated by response due to pressure.

3. Variation in the responses may depend on the location of the lesion within the cerebrum.

4. A study of the operative and necropsy findings will be of material aid in correctly interpreting subsequent responses due to a supratentorial tumor.

THE TREATMENT OF CHRONIC EMPYEMA*

CARL A. HEDBLOM

Although empyema has been recognized and treated for twenty-six centuries, it is only sixty years since a sound rib first was resected for drainage. During the next thirty years attention was directed solely toward collapsing the thoracic wall for obliteration of the cavity. The most radical stage was reached in the complete Schede resection. Since that time the trend has been toward increasing conservatism, the first real contributions in this direction being those of Delorme and Fowler. It has also become more clearly and generally recognized that there is a considerable variability in the pathoogic and clinical aspects of the disease.

The first essential to a consideration of treatment is a clear conception of the cause of chronicity and of the pathology involved. Since chronic cavities and residual sinuses are often but different stages in the same case, the two conditions are considered together. It should be recognized, however, that each may exist independently.

The most common causes of persistent fistula, apart from chronic cavities, are osteomyelitis of the rib, bronchocutaneous fistula, extreme sclerosis of the walls of the sinus, foreign bodies, and, occasionally, tuberculosis. The common causes of a persistent cavity are inadequate drainage; pneumothorax, whether from early open drainage or from a ruptured subpleural abscess resulting in more or less complete collapse of the lung not yet fixed by adhesions; too late drainage after the lung has become fixed firmly in a collapsed position; persistent bronchial fistulas; the presence of foreign bodies; reinfection; and tuberculosis. Of all these factors insufficient drainage is the most common. As a result of the prolonged suppuration a pyogenic membrane which may be 1.25 cm. or more thick is formed. This membrane tends to prevent expansion of the lung even after the primary cause is removed. Treatment should naturally be designed, so far as possible, to remove the cause. Dependent drainage and removal of necrosed rib or foreign material are simple procedures, yet they often bring about a cure after years of chronicity. If a bronchial fistula is present its closure is usually a prerequisite to healing.

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* Abridgment of Thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Surgery, 1920.

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The historical review of the literature (twelve pages) and the bibliography (seven pages) are herewith omitted.

The pathologic condition often can be recognized only in part. Conditions of the lung with respect to tuberculous and other sclerotic changes are often difficult to determine. If an extensive pulmonary tuberculosis is present, or if the bacilli are demonstrated in the pleural exudate, or the typical microscopic picture is found in the sectioned pleura, the diagnosis is established. A history of a primary pleurisy with serous effusion, later becoming purulent, is also at least very suggestive. Often, however, the history and findings are indefinite and uncertain. Primary tuberculous empyema, secondarily infected by injudicious drainage or from within may present a typical picture of the ordinary suppurative pleurisy.

Whether or not the lung is capable of expansion is difficult to decide with any certainty. Various methods to ascertain this have been described, mostly based on a decrease in the size of the cavity during forced expiration. Obviously such a determination may be more a measure of the relative rigidity of the thickened pleura than the elasticity of the lung. Reineboth's ingenious method, depending on the changes in pulmonary circulation that result in increasing the intrapulmonary pressure in a lung that is still expansible but in which changes do not occur if expansibility is lost, unfortunately has not so far proved of practical value. The mechanism by which a collapsed lung expands is of much practical importance and the subject of much difference of opinion. The presence of an intrapleural pressure less than atmospheric and the reason for this so-called "negative" pressure is an elementary fact in physiology. It is also recognized that if an opening is made into the pleural cavity, the lung collapses from equalization of pressure on the two sides of the lung alveolus. Other factors of the first importance to the clinical application of these fundamentals until recently have received but scant attention. Among such factors are the size of the opening in the chest wall in relation to the size of the glottis, the presence of adhesions between the lung and the chest wall, the mobility of the mediastinum, and the vital capacity. The importance of the relationship between the opening in the chest wall and the glottis was recognized by Houston. He asked Van Swieten if a person wounded in both sides of the thorax would die. On being answered in the affirmative Houston produced a small normal dog on which he had opened both pleuras three days before. This astonished Van Sweiten, who repeated the experiment and was persuaded that when air entered the two pleural cavities the wounds were fatal only if the two openings combined were larger in area than that of the glottis. Later Cruveilhier repeated these experiments. It remained for Graham and Bell, however, to point out the great importance of the relationship to the treatment of acute empyema. They showed that in acute cases, owing to the mobility of the mediastinum, the two pleural cavities react as one to changed intrathoracic pressure. Lowering or neutralizing the negative pressure on the one side changed the pressure the same on the other side. Graham showed that the absolute size of an opening in the chest wall, compared with that of the glottis, depends on the vital capacity at the time. Thus a man with healthy lungs can withstand a much larger opening than one with pneumonia or poorly developed lungs.

These considerations are of fundamental importance in the treatment of empyema. The large number of variables involved explains at least in large measure the apparently divergent experiences and opinions on the subject of acute pneumothorax. In chronic empyema, because of the fixation of the mediastinum and the presence of pulmonary adhesions, the two pleural cavities function independently. For this reason a wide opening on the affected side does not produce respiratory insufficiency.

The mechanism by means of which the lung reëxpands has been variously explained. Roser held that it was by the progressive growth of adhesions along the margins of the cavity, the contraction of which pulls out the lung. Weissgerber, on the other hand, held that lung expansion is due to increased intratracheal pressure during expiration, resulting in a summation expansion of the lung. The different conceptions are reflected in the variety of devices for increasing the intratracheal tension on the one hand and for decreasing the tension in the pleural cavity on the other. More recent opinion is also divided. Physicians still use pleural suction. Perhaps the majority, however, are of the opinion that the lung, when free, expands essentially because of the increased tension from within the bronchi, during coughing, straining, or other effort involving closure of the glottis, and that closed drainage, valve action, a pus soaked dressing, and the like are used chiefly in helping to hold the amount of expansion gained. There is much clinical evidence also indicating that progressive adhesions help to hold the lung out, once it is expanded.

Some surgeons believe that adhesions are always detrimental. Thus Lloyd, on the principle that the adhesions tend to prevent expansion, routinely separated them at operation. He reported cases of 225 patients treated in this manner, but with less than 50 per cent complete cures and 20 per cent mortality. Homans has expressed the belief that adhesions in the early stage are often the cause of chronicity but that fixation of the lung to the diaphragm favors expansion.

In chronic empyema the greatly thickened membranes prevent the action of the mechanism which brings about expansion of the lung. If these membranes are removed, incised, or disintegrated, the same mechanism again comes into play, provided the lung has retained its elasticity.

At operation it is often observed that when the patient coughs or strains the liberated lung expands in response to the increased intratracheal pressure. In the after treatment, as in the acute condition, the same factors favor permanent expansion. In the cases in which cavity obliteration occurs following the liberating action of Dakin's solution, it can be determined when operation is performed for a small residual cavity, that the lung is adhering progressively at the periphery of the cavity. Dunham observed at necropsy, in cases in which Dakin's solution was used, that the walls of the cavity were covered with granulations favorable for adhesions, while in those in which there was no treatment a shaggy fibropurulent deposit was found. In case of reinfection these adhesions tend to break down and the cavity enlarges.

Tuffier, Stevens, and others have reported series of cases in which, after sterilization, the tubes were withdrawn and the pneumothorax left to itself, but this method has resulted in many recurrences. If the treatment is successful, the lung apparently expands in proportion as the air absorbs, but in some instances cavities have persisted for months. It seems reasonable to believe that such treatment is more suitable in recent cases than when the condition has persisted for years. To what extent an increasing pulmonary circulation, incident to deep breathing exercise and other effort, aids in bringing about expansion can not be stated, but some experimental evidence has been found to indicate that an increased circulation in the capillaries tends to expand the lung alveolus.

In cases of tuberculous empyema a large cavity may persist for years without any tendency toward lung expansion. At operation in some such cases it is found that the pleura is not appreciably thickened; the failure to expand is probably due to a fibrosis of the lung by which it has lost its expansibility. Fibrosis seems to occur also in long-standing pyogenic empyema.

Aside from considerations of etiology and pathology, the guiding principle in the choice of treatment should be conservatism. Chronic empyema is not necessarily incompatible with years of life and usefulness. In such cases it may be questioned whether radical treatment involving considerable loss of function is ever indicated. It would certainly seem difficult to justify a high mortality, particularly if a safer and more effective method is available. Shortening convalescence is often mentioned as one of the arguments for a radical procedure, but it seems that shortening convalescence does not justify an increased mortality. In the choice of a method of treatment the first consideration, therefore, should be the life of the patient, the second, the preserving of function, and the third, the shortening of the convalescence.

CLINICAL STUDY OF CASES AT THE MAYO CLINIC

In forty-nine of 150 cases of empyema at the Mayo Clinic prior to 1910, the Estlander operation was performed, in nine, the Schede resection, and in one the Delorme decortication. One death occurred following a Schede operation. The 210 patients with empyema treated between 1910 and November, 1917, had more or less extensive rib resections. A Schede operation was done in six instances, a decortication in seven, and Ransohoff's discission of the pleura in one. There were fourteen deaths; one followed a decortication.

During a little more than two years beginning November, 1917, 150 patients with chronic empyema have been treated in the clinic, with a few exceptions, by the writer. Eight of these patients had sinuses only, some of which, however, were fairly extensive. The others had chronic cavities, varying in capacity from 50 to 2500 c.c. One hundred seventeen of the series had been operated on elsewhere. Most of the others came with large accumulations of pus, variously diagnosed. One boy presented himself for the treatment of an extreme scoliosis due to unrecognized empyema of probably eight years' duration. One had been given up as a hopeless case of malignant disease. Unresolved pneumonia and abscess of the lung were diagnosed in many of these cases. Fifteen had tuberculous empyema. Judging from the history, clinical findings, and course, thirteen others may also have been tuberculous. One case of actinomycotic empyema is not included.

It may be noted that three months are taken arbitrarily as the time limit between acute and chronic empyema. In some patients in the series, not previously operated on, the date of onset had to be approximated from the history. In many of the others, in which the duration was calculated from the date of a late operation, it was probably considerably longer than stated. The duration of the empyema by periods and the number of cases in each is indicated in Table 1.

TABLE 1.—DURATION OF EMPYEMA

	Cases
3 to 5 months	38
6 to 12 months	47
13 to 24 months	30
2 to 3 years	12
3 to 5 years	7
5 to 10 years	11
10 to 15 years	3
15 to 20 years	1
More than 20 years	1
	150

TABLE 2.—AGE

	Patients
Less than 5 years	6
6 to 10 years	5
11 to 15 years	6
16 to 20 years	24
21 to 30 years	58
31 to 40 years	34
41 to 50 years	9
51 to 60 years	7
66 years	1
	150

Only eleven were children under 10, yet five of the unrecognized cases were in this age group. In one of these the diagnosis had been first diphtheria, then scarlet fever, and finally typhoid fever.

TABLE 3.—OCCUPATION

	Cases
Farmer	54
Business man	23
Laborer	11
Housewife	9
Student	10
Carpenter	6
Machinist	5
Soldier	3
Miner	3
Railroad man	9
None	6
Not stated	2
Miscellaneous	9
	150

The occupation seemed to bear no obvious relation to incidence.

In nineteen cases there was a fairly definite family history of tuberculosis. Alcoholism in moderation was noted in thirty-seven, and in excess in three. A past history of pneumonia was given in 105, in several of which there had been more than one attack. Pleurisy had been present in association with pneumonia in sixty-four, and was primary in sixteen. A serous effusion followed pneumonia in two definitely tuberculous cases. In eight instances of primary effusion a definite diagnosis of tuberculosis could not be made, but several of these cases ran a clinical course characteristic of a tuberculous empyema secondarily infected.

TABLE 4.—CHIEF COMPLAINTS

	Cases
Draining sinus	87
Pain in chest	22
Weakness	11
Fever	7
Cough	9
Abscess of lung	6
Edema	4
Arthritis	4
	150

The history of onset was given as sudden in 108 cases, insidious in thirty-two, and not stated in ten. The etiologic factors stated in the history were as follows:

Table 5.—Etiologic Factors

	Cases
Pneumonia	65
Pleurisy	15
Influenza	38
Trauma	8
"Cold"	6
Not stated	7
Miscellaneous	11
	150

Pain was a definite symptom in sixty-five; it was localized in the thorax in fifty-seven and in the joints in four, and associated with respiration in six. Marked weakness was noted in fifty-five; cough was present in seventy, absent in twenty-eight, not stated in thirty-two, and was associated with sputum in sixty. The sputum was profuse in eleven; 500 c.c. in three, and 1000 c.c. in two, these being cases of bronchial fistula. Dyspnea and pallor were noted in thirty-six and weakness in fifty. Hemoptysis was noted in four. Loss of weight was a fairly prominent symptom.

Table 6.—Loss of Weight

	Cases
Less than 10 pounds	6
11 to 15 pounds	7
16 to 20 pounds	14
21 to 30 pounds	14
31 to 40 pounds	12
41 to 50 pounds	2
51 to 60 pounds	3
61 to 70 pounds	2
None	10
Amount not stated	34
No mention	46
	150

Fever was present in seventy-five cases, and associated with chills in twenty-two. There was a leukocytosis in two-thirds of the cases in which a count was recorded. The average counts were as follows:

Table 7.—Leukocytosis

	Cases
10,000 to 12,500	28
12,500 to 15,000	17
15,000 to 20,000	20
20,000 to 25,000	14
25,000 to 30,000	5
30,000 to 40,000	2
None	45
Not stated	19
	150

A persistent high leukocyte count was frequently observed in the cases in which Dakin's solution treatment was used without fever or other symptoms of toxic absorption. A secondary anemia was present in the majority of patients, and to a considerable degree in about a third. The averages in 126 were as follows:

Table 8. –Hemoglobin

	Cases
40 to 50 per cent	10
50 to 60 per cent	30
60 to 70 per cent	46
70 to 80 per cent	36
80 to 90 per cent	4

A low blood pressure indicative of an asthenic condition was noted more often than a high pressure. No significant variation was found between systolic and diastolic pressures.

Table 9.—Systolic Blood Pressure

	Cases
80 to 90	3
90 to 100	15
100 to 110	24
110 to 140	77
140 to 160	5
160 to 180	1
Not stated	25
	150

The urinalysis indicated only a relatively small number of cases with kidney involvement, even though the average duration was more than one year in sixty-five of the cases. On the basis of the terminology used in the Mayo Clinic, "albumin 1" signifies the slightest possible trace demonstrable. The albumin content was found to be as follows:

Table 10.—Albuminuria Graded 1 to 4

	Cases
Grade 1	66
Grade 2	25
Grade 3	1
Grade 4	1
None	43
Grade not stated	14
	150

Bacteriologic studies of the exudate at operation revealed the usual bacterial flora. Except for tuberculous infection, there appeared to be no clear relationship between the type of organism and the severity or course of the process in these chronic cases.

The right side was involved in eighty cases and the left side in seventy. The most constant physical signs aside from the presence of a sinus were dullness and flatness to percussion in varying proportion and degree. Dullness was noted in eighty-three and flatness in sixty-two.

Limitation of respiratory excursion was found in the majority of cases.

Fremitus was noted in the area involved in eight cases. Clubbing of the fingers was stated to be present in nineteen and clubbing of the toes in one. The heart was displaced to the right in fifteen; and to the left in nine. A palpable liver and spleen, indicative of a degeneration, was noted in five and six cases respectively.

The clinical diagnosis of the presence of empyema presented little difficulty. A typical empyema is most apt to be overlooked in children. Occasionally an encapsulated empyema with a large bronchial fistula may be quite difficult to distinguish from an abscess of the lung. In some cases, as in one of this series, both were present. In other cases in which there is a history of cough with large amounts of sputum, the differentiation may be impossible without x-ray. Three patients in this series with such symptoms had been treated for months for abscess of the lung. In one instance an empyema had persisted for years without breaking through either lung or chest wall. One case of typical empyema necessitates simulating an acute mastitis was observed. The clinical diagnosis supported by the x-ray examinations in this series was as follows:

Table 11.—Clinical Diagnosis

	Cases
Chronic empyema	115
Effusion or empyema with tuberculosis	9
Empyema with pneumothorax	7
Empyema with bronchial fistula	8
Empyema or abscess	3
Pleural effusion	5
Pneumonia	1
Dermoid cyst	1
Echinococcus cyst	1
	150

It will be noted that a diagnosis of tuberculosis was made clinically in nine of the cases, but the tuberculous lesion was in the lung in five; a tuberculous effusion was specified in four. A diagnosis of a pulmonary lesion was made in three additional cases by the roentgen ray. One of these and two others were proved microscopically. All of these patients gave a history of pleurisy with effusion. Thirteen other patients gave a similar history of a primary pleurisy with effusion. Four of these patients were later proved to have a tuberculous infection of the pleura. Three who were shown by the roentgenogram to have pulmonary involvement clinically responded very well to treatment; the other two reacted in a manner characteristic of a tuberculous empyema. From these findings it appears that while both a pulmonary lesion and a history of a preceding pleurisy with effusion are

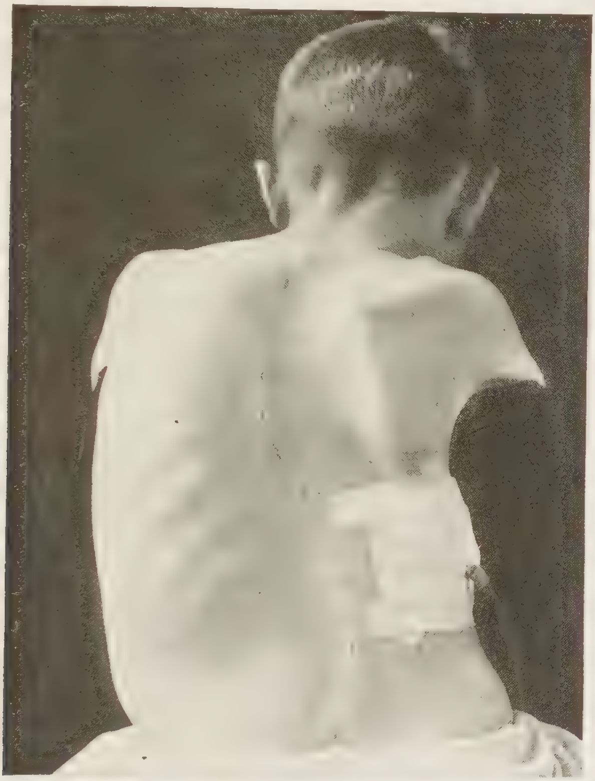

FIG. 175 (Case 269926).—Unrecognized empyema probably of eight years' duration; cavity obliterated by Dakin's solution treatment and minor drainage operation.

important in the differential diagnosis of a tuberculous empyema, a pleurisy with effusion is probably the more significant. A tuberculous empyema may run its course without any clinical or roentgen findings to suggest the condition (Fig. 175).

The choice of surgical treatment for chronic empyema has been between simple drainage and some type of operation designed to collapse the chest wall or to expand the lung. In the earlier cases in this series, if a cavity or any size persisted, simple drainage was first tried, followed by a decortication. In the autumn of 1918, Dakin's solution was first used in an attempt to obtain partial sterilization of the cavity before a decortication or plastic operation was performed. It was then discovered that not only the patient's general condition was improved greatly, but the cavity showed an unmistakable tendency to reduce. The solution was then used systematically and an extensive operation performed only after the hypochlorite solution treatment had been tried. If operation was indicated for a cavity of considerable size in a nontuberculous case, an attempt was made routinely to obtain expansion of the lung before a collapse operation was performed.

Methods of treatment.—The methods of treatment were as follows: (1) simple rib resection, forty-two cases, (2) Dakin's solution with or without minor drainage operations, fifty-one cases, (3) pulmonary decortication, thirty cases, and (4) plastic operation on the chest wall, twenty-seven cases.

1. *Simple rib resection.*—Thirty-four of the forty-two patients in this group had been operated on elsewhere. Many of them had undergone several, and one eleven drainage operations. Among those who had not had previous operations, there were several with large cavities. Two had bronchial fistulas and were emptying the contents of a large cavity through the bronchus. Two had drainage tubes in the pleural cavity, the presence of which had been unsuspected. Faulty drainage was the rule; the drainage opening had been allowed to close or narrow down to a sinus before the cavity had become obliterated, or the opening was not at the most dependent point. The capacity of the cavity in this group was less than 250 c.c. in twelve, between 250 and 500 c.c. in eight, and near 1000 c.c. in two; in one the lung was almost wholly collapsed.

The results of simple drainage operation, not counting the tuberculous cases, were: complete recovery, twenty-six cases, persistent sinus at last report, four cases, and death, one case. Eight patients could not be traced. Of the tuberculous patients one was greatly improved, one somewhat improved, and one was not benefited. All three had been drained previously elsewhere.

2. *Dakin's solution with or without a minor drainage operation for a small residual cavity.* —There were fifty-one cases in this group. The technic employed consisted in the insertion of a catheter through the old sinus or through a trocar and cannula, aspirating the pus and irrigating with the sodium hypochlorite solution. As a rule, normal saline solution was used for the first irrigation, and if there had been cough with sputum it was used always in order to avoid the marked bronchial irritation if a bronchial fistula should be present. Irrigation was performed at intervals of from one to three hours. Once or twice each day the cavity was half filled with the solution, which was aspirated after about ten minutes. Once a week the cavity was filled by gravity and the capacity noted. In this way progress was measured. The patients were encouraged to use blow bottles and other devices to produce increased intratracheal pressure. While they were blowing the catheter was connected with a tube, the other end of which was under water in order to allow the air to escape as the lung expanded and to prevent its return. The patients were given setting-up exercises and encouraged to be out doors as much as possible besides. A generous diet was prescribed.

TABLE 12.—RESULTS OF DAKIN'S SOLUTION TREATMENT IN FIFTY-ONE CASES

Capacity of cavity, c.c.	Average number of days of treatment	Capacity of cavity at end of treatment, c.c.	Average decrease in capacity of cavity, per cent	Cases
Less than 100	35.9	10	90.0	11
100 to 250	34.1	11 to 27.5	89.0	16
250 to 500	56.4	11 to 22.0	95.6	15
500 to 1000	45.2	11 to 22.0	97.8	5
1000 to 2000	32.0	80 to 160	92.0	4

	Cases
Complete recovery	34
Sinus at last report	6
No late report	6
Convalescence not completed	4
No benefit (tuberculosis)	1
	51

A large portion of the time spent in treatment was for the final obliteration of a cavity after it had been reduced 50 to 75 per cent (Figs. 176 and 177).

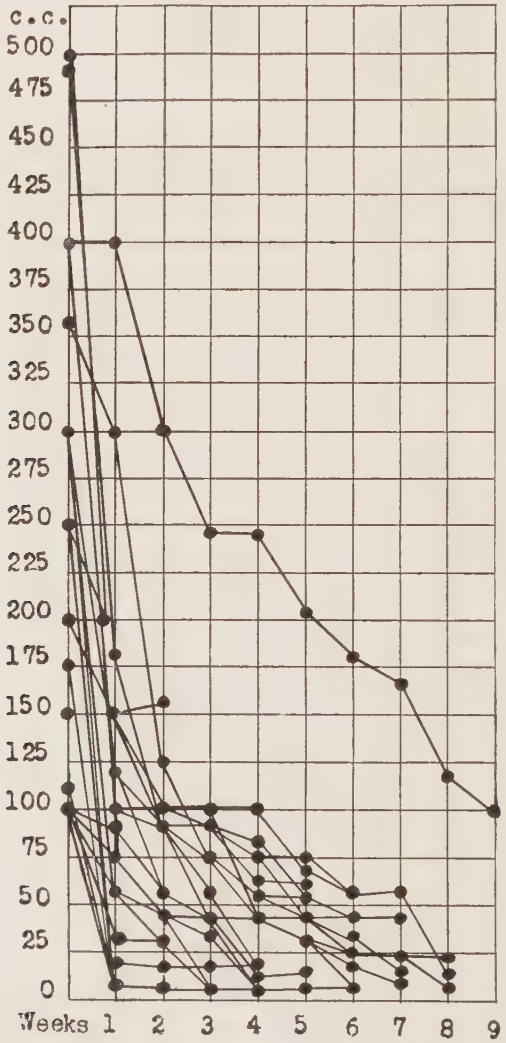

FIG. 176.—Twenty-eight cases, capacity from 100 to 500 c.c.

Besides the reduction in the size of cavities of more than 90 per cent, there was a striking general improvement in all these patients. A gain in weight of from 1 to 2 pounds each day for a period of two or three weeks was frequently observed. A slight amount of bleeding and occasionally some cough were noted, but no serious complications. The hypochlorite solution was used in fifteen patients preliminary to pulmonary decortication. Six were treated for a period not exceeding three weeks, all of these showing an appreciable decrease in the size of the cavity. In the cases, with one exception, there was also a material decrease (Figs. 178-186).

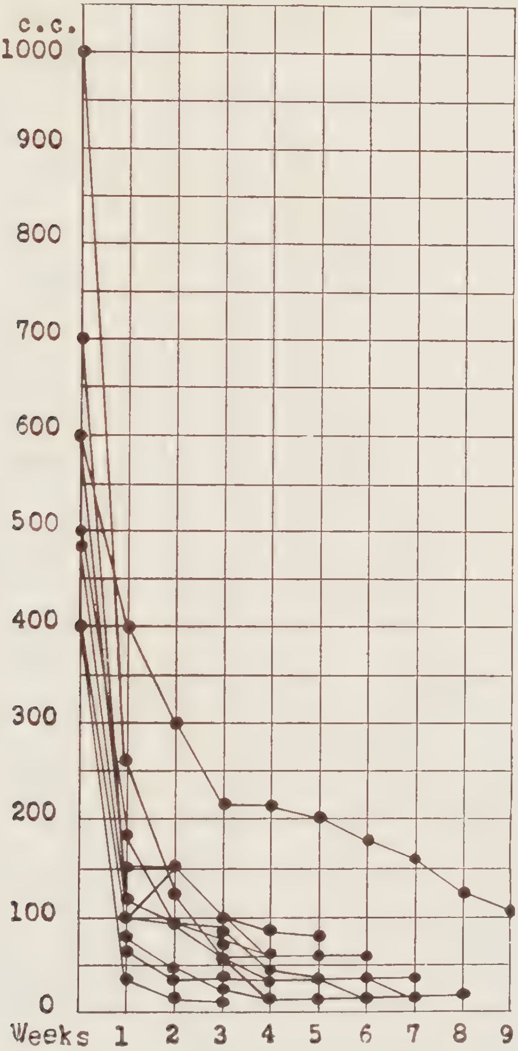

FIG. 177.—Ten cases, capacity from 400 to 1000 c.c.

TABLE 13.—RESULT OF DAKIN'S SOLUTION TREATMENT PRELIMINARY TO DECORTICATION IN FIFTEEN CASES

Capacity of cavity, c.c.	Duration of empyema, months	Days of treatment	Capacity of cavity at end of treatment, c.c.
360	6	9	210
500	20	10	200
200	21	12	100
500	6	12	180
240	4	19	150
300	4	21	240
150	3	27	150
420	15	30	390
1000	14	32	90
150	7	42	15
1500	3	43	100
400	4	46	30
500	6	70	60
2000	6	75	120
2000	14	150	240

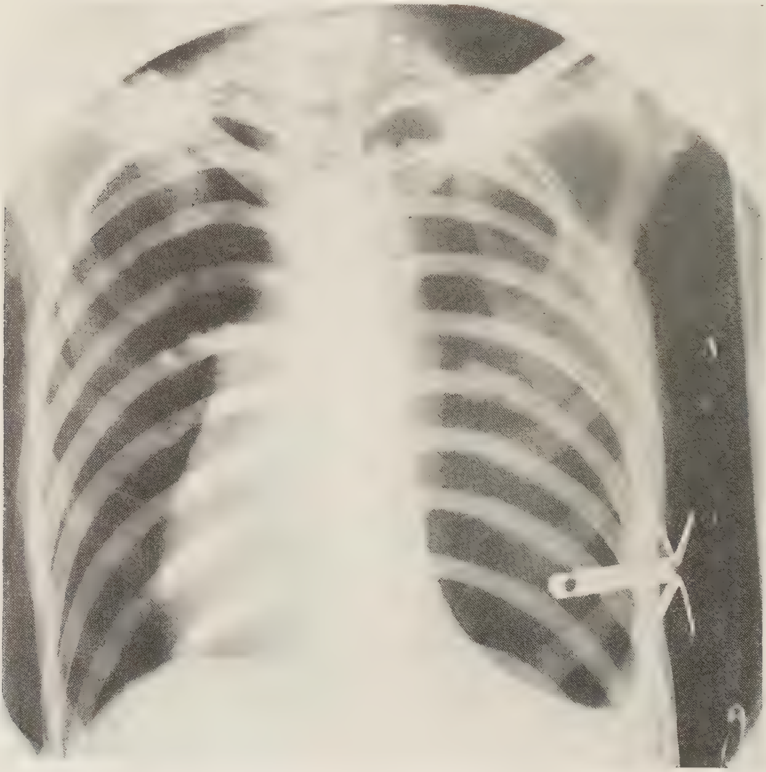

FIG. 178 (Case 261485).—Traumatic empyema of four months' standing; fracture of ribs; almost complete collapse of the lung before Dakin's solution treatment. Patient's weight, 73 pounds; normal weight, 125.

Several of the patients in this series would not have withstood an operation of any magnitude without the preliminary treatment. One was a girl with complete collapse of the lung following traumatic empyema. She was reduced from 120 pounds to 73 pounds and was brought to the clinic on a stretcher. She was completely cured with almost full reëxpansion of the lung. Another patient had an almost total pneumothorax, a complete inhibition Wassermann reaction and a severe grade of nephritis with edema. His blood was rendered negative to the Wassermann test, his lung reëxpanded about 90 per cent, and he gained about 30 pounds as a result of the preliminary treatment.

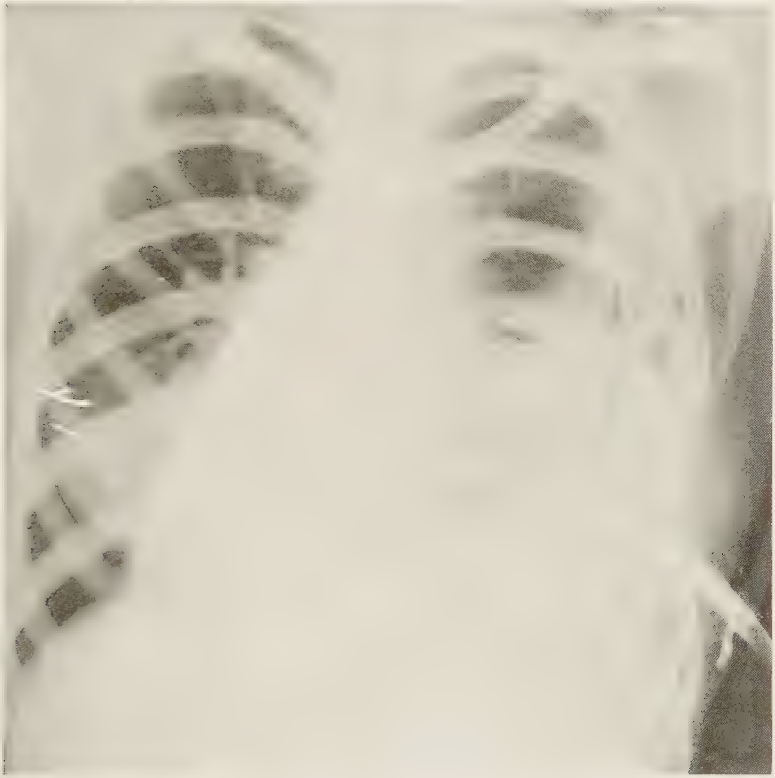

Fig. 179 (Case 261485).—Full expansion of the lung at the apex of empyema cavity shown in Figure 178 after about four months' treatment. Complete cure followed plastic operation on residual cavity.

3. *Pulmonary decortication.* —There were thirty cases in this group. The operation, except in some early cases before Dakin's solution was employed as a routine, was performed only after the antiseptic method had been used and a large cavity remained. In a few of the early cases, only, the cavity was comparatively small. In these cases in which it failed to obliterate, it had been rendered relatively sterile, and the patient's general condition was very materially improved.

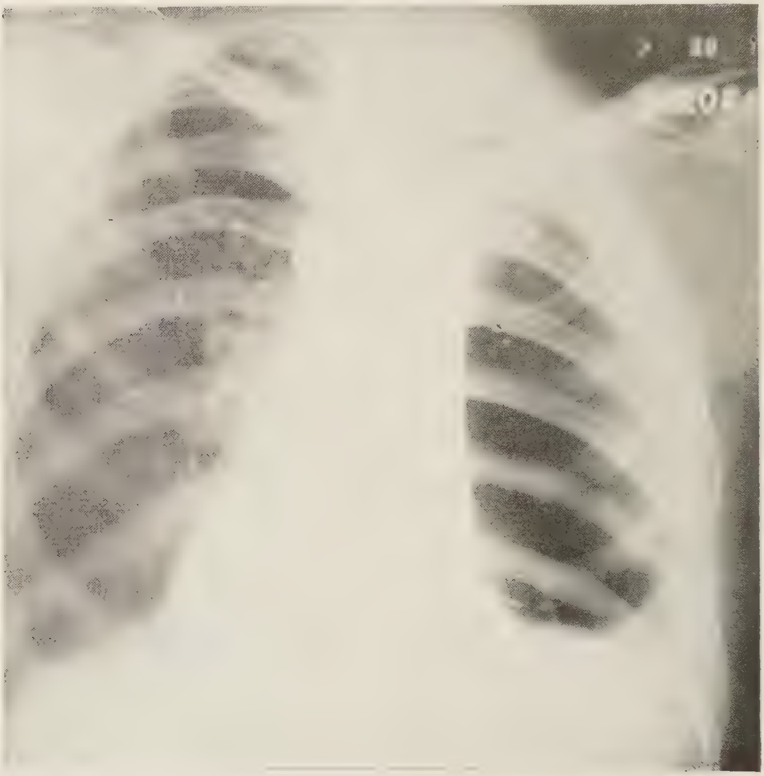

FIG. 180 (Case 282026).—Chronic empyema of eighteen months' duration; with massive collapse of lung; chronic nephritis with edema, and complete inhibition Wassermann test.

Decortication was done under general anesthesia through a rib-spreading exposure. By use of a suitable rib retractor, adequate exposure was obtained without cutting the ribs. In some cases in which the cavity lay very high, incision was made in the sixth or fifth interspace, cutting the scapula across and resuturing it. Possibly resection of the ribs posteriorly would have been a better procedure. The thickened visceral pleura was incised and separated by blunt dissection. In many cases the preliminary irrigation had softened it to such an extent that the separation could be done very readily.

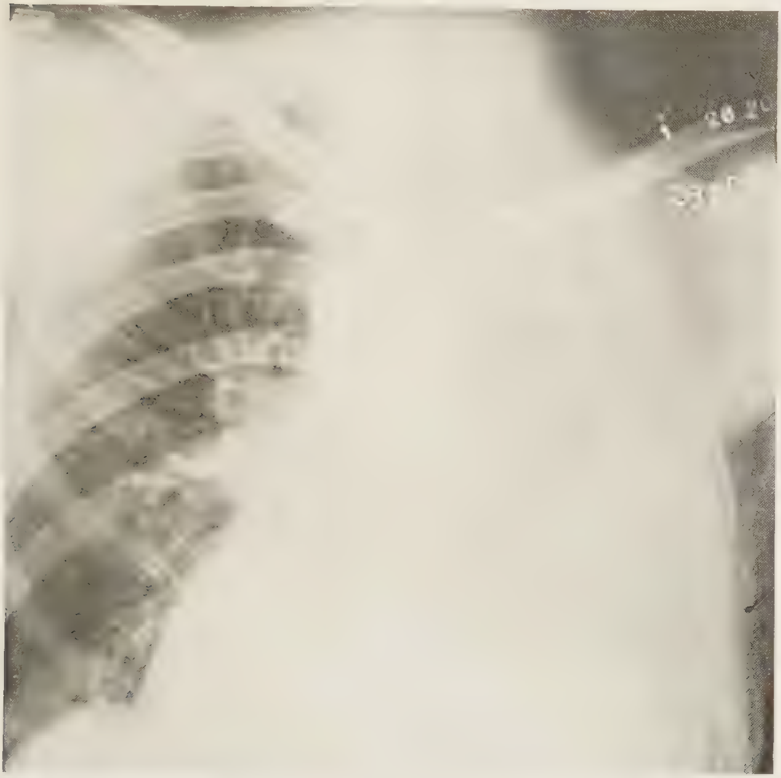

Fig. 181 (Case 282026).—Lung shown in Figure 180 partly expanded; Wassermann negative, and patient gained 30 pounds in weight.

If cavities were large a complete visceral decortication was done, mobilizing the entire lung. In one case only, of primary tuberculous empyema, it was absolutely impossible to separate or satisfactorily to incise it, but partial obliteration of the cavity was secured by mobilizing the lung, as first suggested by Souligoux.

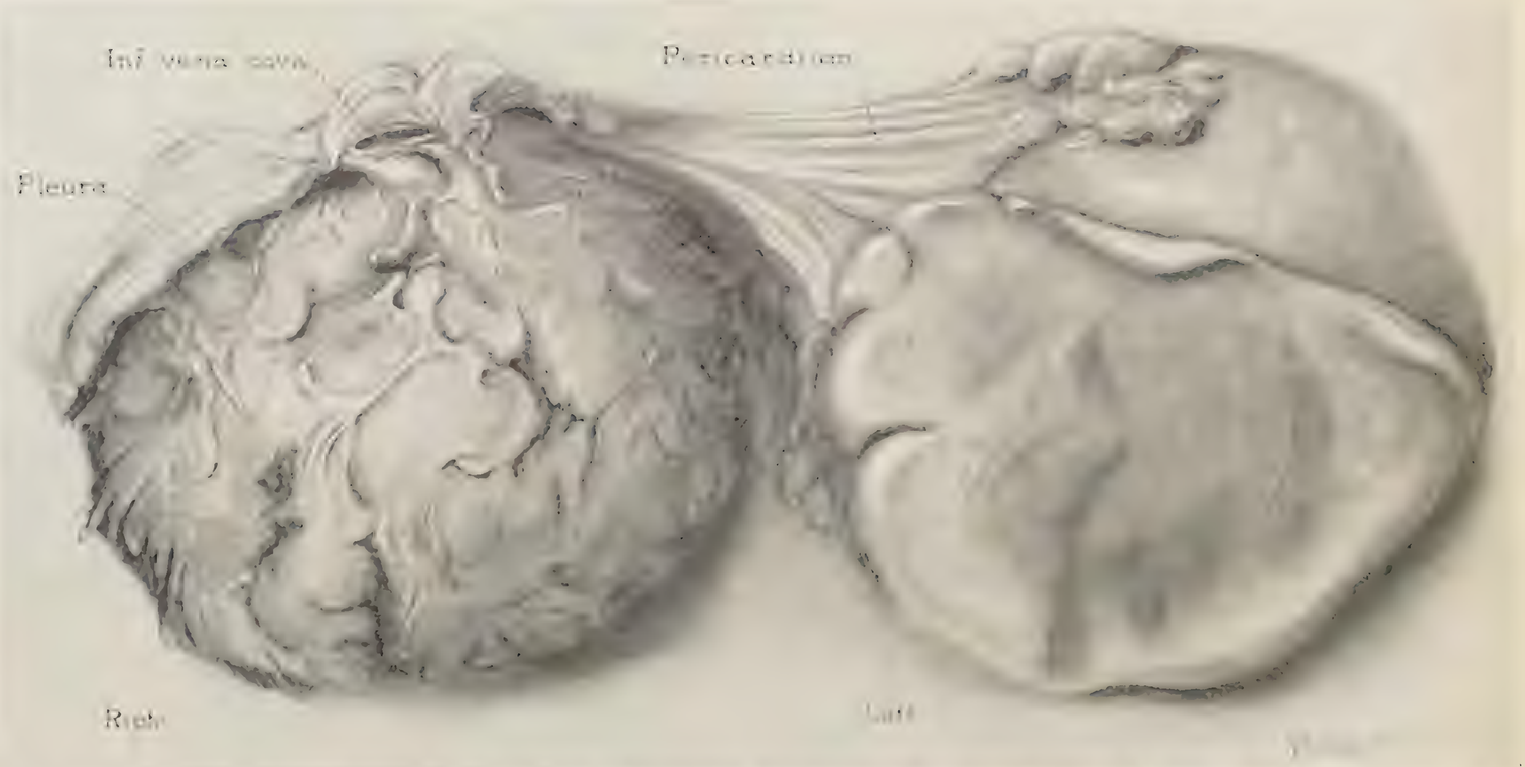

Fig. 152 (Case 30,153).—Partial expansion of lung following decortication for empyema, after complete collapse of sixteen months. The patient died of epidemic streptococcus bronchopneumonia three days after operation.

Table 14.—Results of Decortication in Thirty Cases

	Cases
Complete cure without further surgery	**15**
Complete cure after secondary plastic operation for small residual cavity	5
Persistent sinus, last report	3
Death following operation	1
Death from other causes several weeks after patient left hospital	3
Under treatment	3

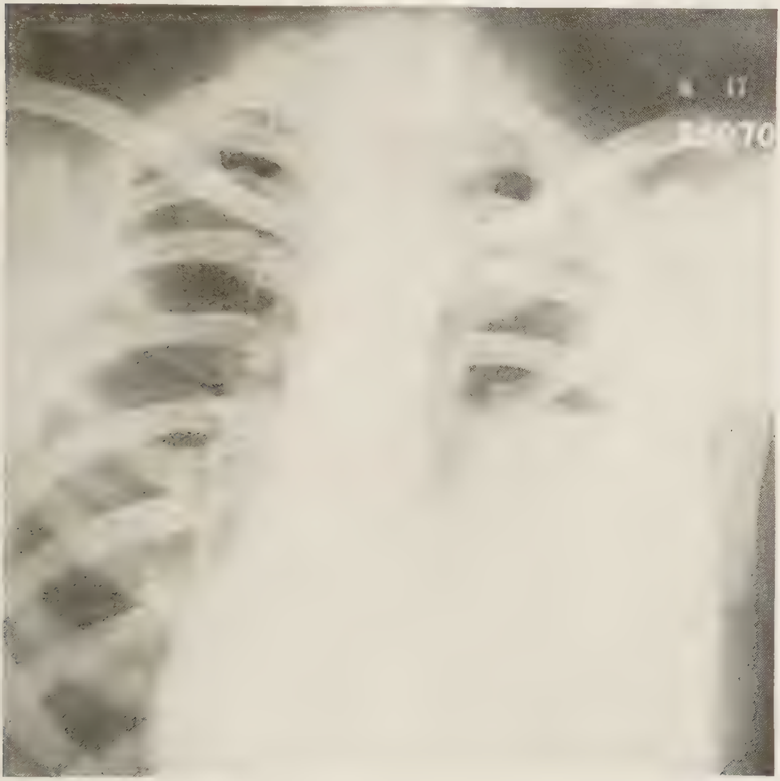

Fig. 183 (Case 260701).—Chronic empyema of four months' standing before treatment.

Two of the three patients with small sinuses were tuberculous. In one of these the cavity was practically obliterated. The patient gained very materially in weight and general condition following operation. The one operative death was due to a streptococcus pneumonia occurring during an influenza epidemic. Two of the patients who died several weeks after operation also had epidemic influenzal bronchopneumonia. Necropsy in one of these showed one lung expanded and an empyema on the other side. The third patient, in whom the cavity had been reduced to about 30 c.c. capacity by operation, died of pulmonary hemorrhage seven months later. Tuberculosis bacilli were found in the exudate and tubercles in the pleura shortly before death. At no time did the x-ray show any evidence of tuberculosis (Figs. 187–91).

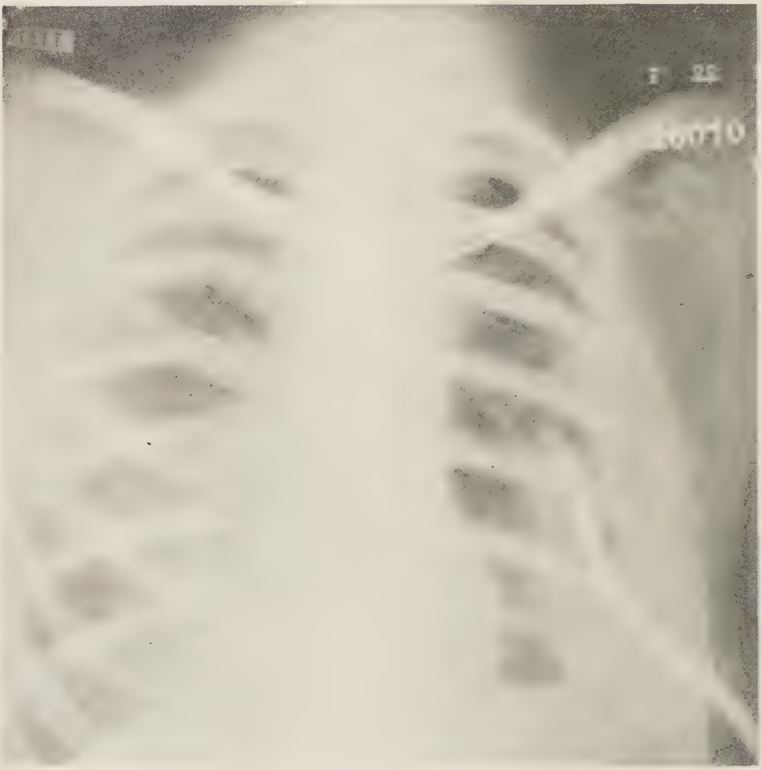

Fig. 184 (Case 260701).—Residual sinus of chronic empyema about nine weeks after decortication. Later cure was complete.

4. *Plastic operation involving the collapse of the chest wall.*—Twenty-seven patients were treated by this method. The duration of the disease was more than one year in twenty-one and more than two years in eleven; in one it was of twenty-three years' duration. Five patients were definitely proved to be tuberculous; two others belonged to the group of primary pleurisy with effusion which ran a course

suggestive of tuberculosis. Dakin's solution was used in eight patients in this group (Fig. 192).

TABLE 15.—RESULTS OF DAKIN'S SOLUTION TREATMENT PRELIMINARY TO PLASTIC OPERATION IN EIGHT CASES

Capacity of cavity, c.c.	Duration of empyema	Days of treatment	Capacity of cavity at end of treatment, c.c.
500	3 months	22	120
150	4 months	55	30
60	3 years	57	45
100	3 years	35	100
200	10 months	30	60
150	1 year	9	150
500	9 months	47	30
750	7 years	90	300

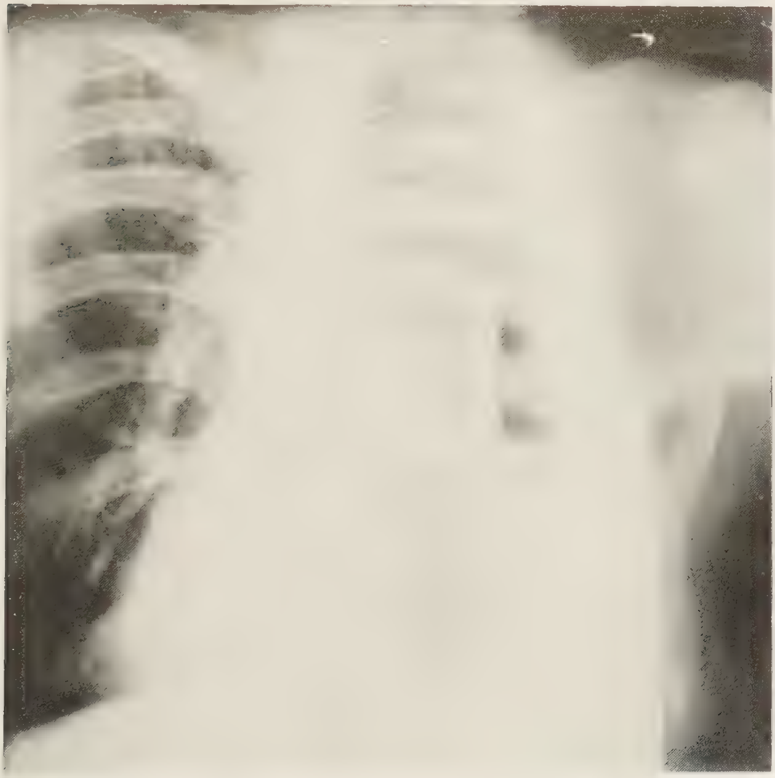

FIG. 185 (Case 185290).—Tuberculous empyema; partial obliteration of the cavity by the use of Dakin's solution treatment.

In nineteen cases the solution could not be used on account of fistulas, or they were cases treated before the solution was used routinely.

The operation involved resection of the ribs over the entire cavity, and with one exception, in which an Estlander operation was performed, excising the intercostal tissue and parietal pleura. A complete Schede operation was not found necessary in any case. The extent of rib resection was reduced in the majority of cases by the skin sliding method described by Beck. In a few instances a skin muscle flap, as recommended by Robinson, was made. Resection of the lower angle of the scapula was necessary in three instances in which the cavity lay

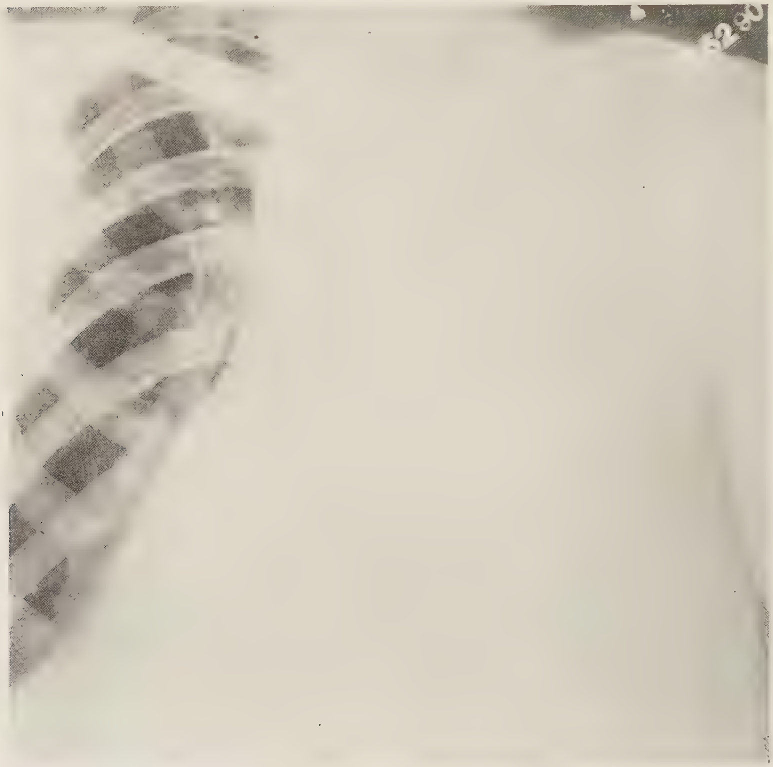

Fig. 186 (Case 185290).—Tuberculous empyema following Wilms' operation for obliteration of residual cavity.

directly under it. In one case of tuberculous empyema of twenty-three years' standing, the whole chest wall was resected en masse, after the method recently described by Peuckert. In another, also tuberculous, the Wilms operation was performed in three stages.

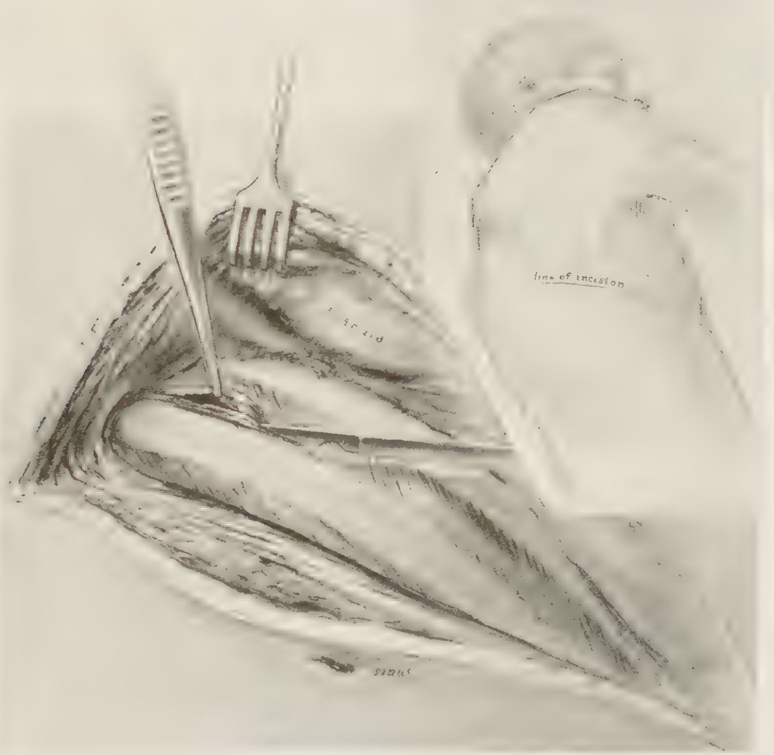

FIG. 187.—Intercostal incision for exploration of chronic empyema cavity.

TABLE 16.—RESULTS FOLLOWING PLASTIC OPERATION IN TWENTY-SEVEN CASES

	Cases
Cure	15
Residual sinus at last report	3
Death	2
Convalescence not complete	4
Not traced	3
	27

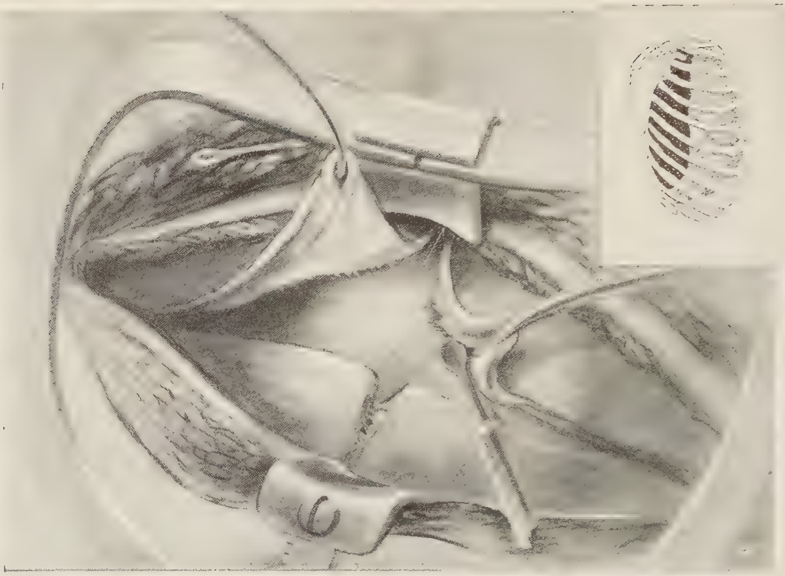

FIG. 188.—Decortication following a crucial incision in the pleura in a case of large cavity. The apex of the scapula has been removed, the ribs being divided in the sixth interspace. Retractor devised by the writer.

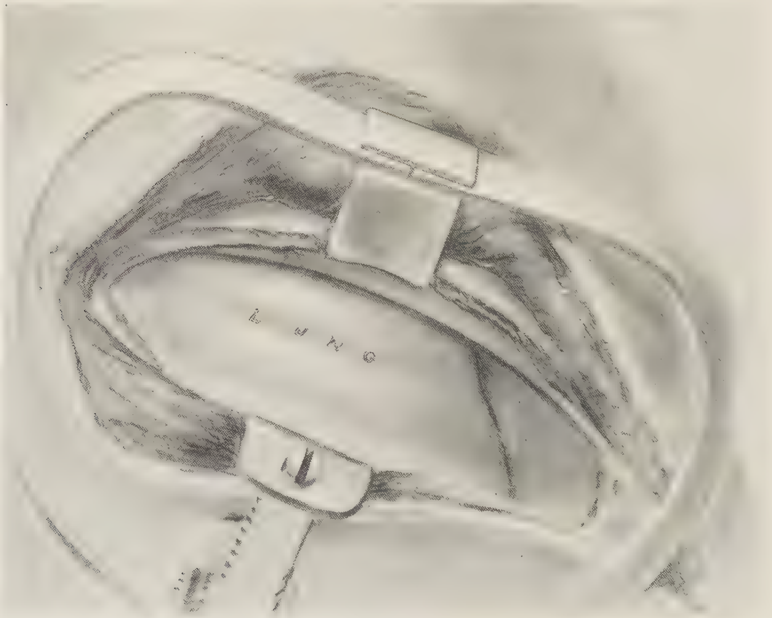

FIG. 189.—Lung expanding with straining of the patient.

Two of the patients with persistent sinuses were tuberculous. In one the sinus closed after many months. In one the sinus was due to multiple bronchial fistulas with an associated bronchiectasis. The closure of bronchial fistulas, as I have mentioned, is necessary to the cure of an empyema cavity.

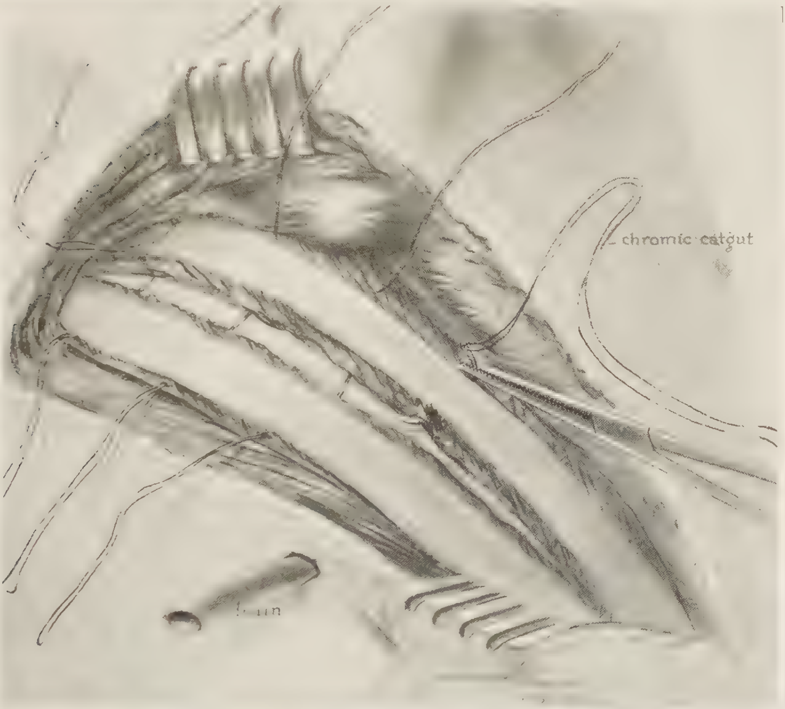

Fig. 190.—Air-tight closure of chest wall. Catheter through old sinus or through stab wound for aspiration and suction.

The cases of bronchial fistulas in this series may for convenience be divided into three groups, namely, those in which the cavity closed spontaneously, those in which it was obliterated by operative procedure and those in which it persisted.

In the first group are a number of cases in which the hypochlorite solution was used. A bronchial fistula was judged to be present if the patient coughed during irrigation and at the same time tasted the solution. In some instances these symptoms were so slight and transitory that the treatment could be continued provided the cavity was not filled. In others irrigation could be done only when the patient assumed a certain posture. Occasionally it was necessary to substitute saline solution for longer or shorter periods. In a considerable number there was slight bleeding from time to time. In no case was the bleeding profuse. In a few the fistulas were observed at operation; they were uniformly small.

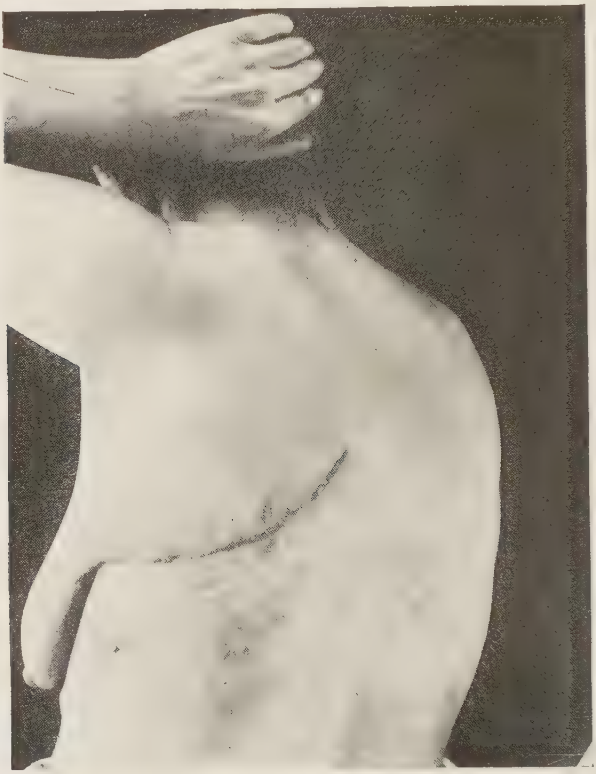

FIG. 191 (Case 251963).—Primary union following intercostal incision for pulmonary decortication. All ribs intact. The patient has free use of her arm.

In the second group are the ten cases in which the fistulas were 0.7 cm. or more in diameter. They were multiple in one case only. Four were due to perforation of large unrecognized empyemas of long standing. These closed after wide open drainage was provided. In one case of ten years' duration a large fistula was found at the costovertebral angle. It was closed by an extensive resection and cauterization of the tract. In another instance, the scar tissue was completely removed and the edges of the fistula sutured after preliminary cauterization. The remaining four fistulas were closed by resection of the ribs and thickened pleura followed by skin plastic.

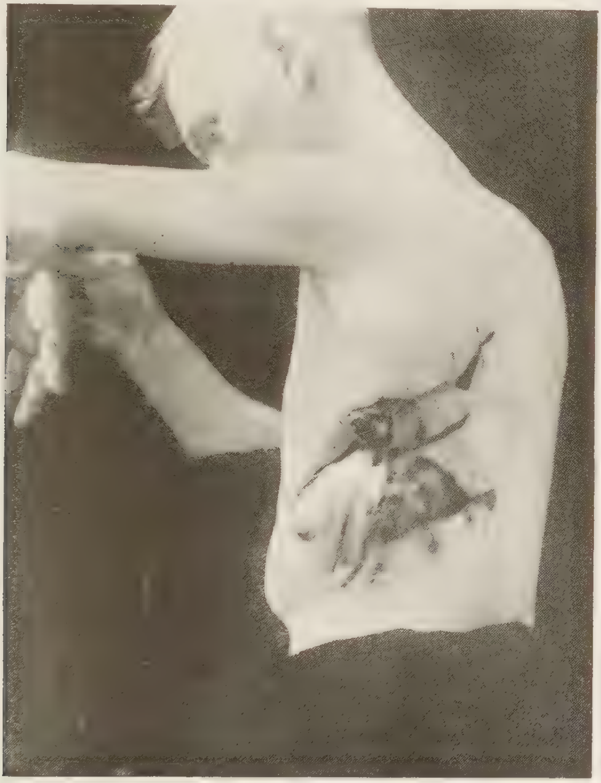

Fig. 192 (Case 214734).—Plastic operation for closure of the chronic cavity.

In the group of cases with persistent bronchial fistulas were two tuberculous cases. In one an unsuccessful partial plastic operation was done; in the other no treatment was given for the fistula. A third patient had twenty or more bronchial fistulas in the same lobe of the lung, with extensive bronchiectasis. Considerable improvement in the general condition and obliteration of most of the fistulas resulted from granulation tissue proliferation after cauterization (Fig. 193).

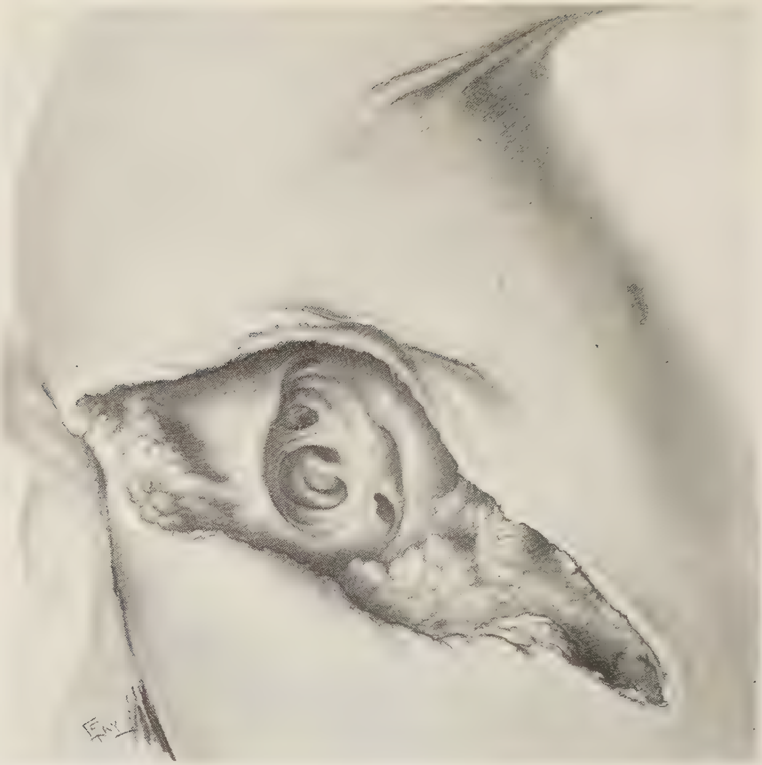

FIG. 193.—Multiple bronchial fistulas in a patient with chronic empyema with bronchiectasis.

RESULTS OF ALL METHODS OF TREATMENT

TABLE 17.—SUMMARY OF RESULTS OF TREATMENT IN 150 CASES OF CHRONIC EMPYEMA

	Drainage operation, cases	Dakin's solution treatment, cases	Decortication operation, cases	Plastic operation, cases	Total cases
Complete recovery	26	34	20	15	95
Residual sinus at last report	6	6	6	3	21
No report, or convalescence not completed	8	10	3	7	28
No relief	1	1	..	..	2
Death*	1	..	1	2	4
Total	42	51	30	27	150

* Besides the patients whose deaths were recorded as operative, four patients died after leaving the hospital, two several weeks after operation from Streptococcus pneumonia; one died seven months after operation from tuberculosis, and one from "meningitis."

Some of the persistent sinuses followed plastic operations for tuberculous empyema, others are in recent pyogenic cases giving promise of complete closure. Practically all nontuberculous sinuses can be obliterated by plastic operation. Since, as experience has shown, however, that the majority of the sinuses heal spontaneously, expectant treatment for a limited period has been considered justified and in many cases advisable.

TABLE 18.—OPERATIVE DEATHS

Cause of death	Operation	Cases
Sepsis and inanition	Rib resection for drainage	1
Cerebral abscess	Plastic operation	1
Tuberculous meningitis	Plastic operation	1
Influenzal pneumonia	Decortication operation	1
		4

CONCLUSIONS

From the study of the literature and of 150 cases from the Mayo Clinic the following tentative conclusions may be drawn:

1. Chronic empyema has been recognized and treated during twenty-six centuries, but it is only sixty years since the first rib resection for drainage was done. The successive stages in the progress of treatment since that time are as follows:

(a) Increasingly radical treatment, designed to obliterate the cavity by the collapse of the chest wall, involving successively more extensive operations, and culminating finally in a complete radical resection.

(b) A conservative trend manifested primarily in the modifications of the complete resection, but more in the attempt to preserve the chest wall and to restore the lung to its structural and functional relationships as first advocated by Delorme.

(c) The adaptation of the Carrel-Dakin hypochlorite solution technic to the treatment of chronic empyema cavities.

2. Chronic empyema is a disease which is not incompatible with life nor with a fair degree of health and usefulness. The principles of treatment should, therefore be, first, the preservation of life, and second, as far as possible, the conservation of function. Shortening convalescence, while very desirable, should always be a subsidiary consideration.

3. The choice of treatment must be made with cognizance of the variable etiology and pathology of the process, and the general condition of the patient.

4. A major procedure is indicated only if nonoperative or less extensive surgical treatment reasonably may be considered less effective.

5. In case of sinuses and small cavities, adequate drainage is usually sufficient to effect a cure with or without short preliminary hypochlorite solution treatment. It is at least open to question whether a radical operation is indicated in these cases for the sole purpose of shortening convalescence at the risk of an appreciably increased mortality.

6. Dakin's hypochlorite solution treatment is the method of choice in the treatment of the ordinary type of chronic empyema cavity of any size, for the following reasons:

(*a*) The general condition of the patient is, as a rule, improved to a remarkable degree.

(*b*) The cavity may be obliterated or greatly reduced in capacity by the liberation and expansion of the lung (resulting from the treatment).

(*c*) If the lung expands in part the extent of a later operation will be proportionately reduced.

(*d*) If the lung entirely fails to expand, the cavity will have become relatively sterile in preparation for operation, thereby lowering postoperative morbidity and mortality.

(*e*) Pulmonary decortication will be materially facilitated in some cases, owing to the softening action of the solution on the visceral pleura.

7. A pulmonary decortication through a rib-spreading exposure after preliminary hypochlorite solution irrigation is the most conservative treatment for cavities that are not obliterated by drainage or Dakin's solution treatment alone. If such an operation is successful the lung is restored to its normal structural and functional relationship, thereby obliterating the cavity. If the operation is only partly successful, the magnitude of a secondary destructive operation is proportionately decreased.

8. Since it is impossible to judge with certainty before operation of the relative expansibility of the lung in every recent nontuberculous

case, a decortication should be done rather than a destructive operation, thereby giving the patient the benefit of the doubt.

9. If the lung does not expand, or if a considerable cavity persists following decortication, a plastic operation is indicated.

10. If the cavity is of considerable extent or the patient debilitated, a two-stage or three-stage plastic operation is to be recommended.

11. The recognition of tuberculous empyema is often difficult. A history of a primary pleurisy with effusion seems more often to signify a tuberculous condition than does a pulmonary lesion, unless the latter is active and extensive. A tuberculous empyema may be present in the absence of clinical or x-ray evidence of pulmonary involvement. The typical microscopic picture in the sectioned pleura or the demonstration of the bacilli in the exudate may constitute the only evidence in such cases.

12. A tuberculous empyema not secondarily infected should not be drained, and should be aspirated only for a considerable accumulation of fluid. For a tuberculous empyema secondarily infected, either by operation or spontaneously, drainage is necessary.

13. In the absence of bronchial fistulas and of bleeding, secondarily infected tuberculous empyema may be markedly benefited by antiseptic solution treatment. The amount of fibrosis or other pathologic change in the lung in such cases determines the degree of expansion of the lung, whether following antiseptic solution treatment or decortication.

14. If the lung fails to expand in whole or in large part, a several-stage operation designed to collapse the chest wall is indicated. Tuberculous patients are relatively poor operative risks.

15. Adequate drainage is the first indication in cases of empyema cavities which are draining through large bronchial fistulas. The fistulas may be obliterated spontaneously following such treatment.

16. Operative closure of bronchial fistulas that persist is necessary to complete healing. It may be accomplished by decortication of the involved portion of the lung with cautery, suture, or skin plastic to cover the opening of the fistula. Occasionally healing results from simple granulation of surrounding tissue after destruction of the epithelial lining of the bronchial stoma.

17. Closing the bronchus that is draining pus from within the lung may result in a secondary lung abscess.

18. A large bronchial fistula is a contraindication to Dakin's solution treatment.

19. Sinuses of variable duration are common following more or less complete obliteration of empyema cavities; a large proportion eventually are obliterated without radical treatment; for those which persist, plastic operation is indicated.

20. Operative mortality in chronic empyema has been due largely to shock and infection. Reduction of the extent of operation and preliminary sterilization will materially lower this mortality.

THE ROENTGENOLOGIC DIAGNOSIS OF PRIMARY CARCINOMA OF THE LUNG*

FRANCIS B. McMAHON

This thesis covers a study of six cases of primary carcinoma of the lung examined at the Mayo Clinic before 1917. In four of the cases diagnosis was confirmed at necropsy; in one case an exploratory operation was performed and diagnosis confirmed by microscopic examination; and in the other case necropsy was not permitted. Previous to this investigation 428 authentic cases of carcinoma of the lung have been reported in the literature. The clinical and physical findings in primary carcinoma of the lung are not markedly different from those in any other chronic lesion in the chest, and the differential diagnosis is best made by roentgen examination.

There are three main types of primary carcinoma of the lung which present characteristic gross pathologic appearances: the infiltrative, the miliary, and the mixed.

Stereoscopic study of the infiltrative type shows one or more areas of increased density along the roots of the larger bronchi. The shadows are homogeneous or partially mottled and the borders are not sharply demarked. The areas of density are wedge-shaped, with the apex pointing towards the hilus. In the early stages the process does not extend to the periphery of the lung. The most frequent site of this type of lesion, which is usually unilateral, is in one of the lower lobes. There is always a hazy shadow-zone surrounding the lesion due to active or passive hyperemia. Two of the cases studied were of this type.

In the miliary type of carcinoma of the lung there are innumerable conglomerate areas of increased density extending throughout the lobe. The borders are poorly defined and not sharply circumscribed.

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* Abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery, 1917.

This thesis was published in full in the American Journal of the Medical Sciences, 1918, clv, 34–47. Copyright, Lea and Febiger, Philadelphia.

The areas are distributed uniformly and there are usually no true cavities. Two of the cases studied were of this type.

The mixed type of carcinoma of the lung includes a combination of the infiltrative and the miliary forms. In this type the lesions are poorly circumscribed, homogeneous, or slightly mottled areas of increased density in one or more parts of the lung, and multiple smaller areas of increased density similar to those found in the miliary type, diffusely studding the entire remaining portions of both lungs. Two of the cases studied were of this type and in both the diagnosis was confirmed at necropsy. These are probably the first cases reported of the mixed type.

The differential diagnosis must be based on a large number of other pathologic conditions found in the thorax, including inflammatory lesions and neoplasms. Among them are bronchiectasis, pulmonary abscess, encysted empyema, pneumonia, syphilis, sarcoma, lymphosarcoma, Hodgkin's disease, actinomycosis, metastatic malignant disease, cysts of the lung, fibromyxoma, tuberculosis, pneumoconiosis, chronic passive congestion, chronic pleuritis, and pleural transudates and exudates.

A careful correlation of the roentgen findings with the clinical history and the physical and laboratory findings usually makes a clinical and differential diagnosis possible.

GROWTH OF THE ABDOMINAL REGION IN THE HUMAN FETUS*

HELEN ADAMS MACKEEN

This work was undertaken to ascertain what changes, if any, take place in the form of the abdomen of the human fetus, and to determine the rate of growth of the various parts of the region as compared with the rate of growth of the body as a whole and with the rate of growth of the trunk region.

Twenty-one measurements were taken on a series of 187, of which the smallest measured was 28 mm. in crown-heel length and the largest 590 mm. crown-heel length. The specimens were well distributed in the series. Seventy-five specimens were male, eighty-seven were female, and the sex of twenty-five could not be differentiated externally.

All measurements were made directly on the specimens; vernier calipers and steel tape were used, except on the very small specimens, on which linen thread was substituted for the steel tape. Measurements were chosen so as to end, so far as possible, on skeletal points recognized as limits of the abdomen. They included, beside the total body length and the sitting height, a series of five measurements on the anterior midsagittal line between the sternal notch and the symphysis pubis; one measurement on the lateral vertical line between the inguinal ligament and the costal arch; one of the vertical distance between the free tip of the twelfth rib and the iliac crest; four of the obstetric measurements of the pelvis, interspinous, intercristal, intertrochanteric and the external conjugate; two on the length of the lumbococcygeal spine; two projections on the anterior midsagittal line of the distance above the symphysis pubis of the iliac crest and the lower margin of the tenth rib; and four circumferences, at the level of the xiphisternal junction, at the level of the lowest point of the tenth rib, at the level of the umbilicus, and at the level of the iliac crests.

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*Abstract of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Arts, 1919.

The figures obtained from these measurements were tabulated and used in the development of ogives and histograms and diagrams of surface outline.

It was noted that although growth progressed at different rates in the different measurements taken, rate of growth for any one measurement was singularly constant, indicating that the rate for the given region measured had been established very early in fetal life, before the 28 mm. crown-heel stage. Therefore, plotting the value of the given measurement against the body length resulted in practically straight lines. Any deviation in the curves may be considered due to an insufficient number of observations, to the element of error introduced through variations in shrinkage of the bodies due to fixation, and to error in making the measurements.

The rate of growth in all measurements save the circumferences, besides being constant throughout intra-uterine development, apparently continues unchecked, at least through the first trimester of postnatal development. An exception has been noted in the curves of the circumferences, which maintain a constant rate of increase up to the 500 mm. crown-heel stage or through normal intra-uterine development, but beyond this stage the rate decreases and the curves tend to flatten out.

Literature relative to pelvic measurements in the newborn child was reviewed and the results tabulated. Especial emphasis was laid on sex differences. Although values vary it was found to be generally conceded that the diameters of the pelvis of the newborn male infant are greater than those of the female newborn. The same measurements in the small series of newborn infants six males, ten females available in preparing this report, yielded opposite results; each measurement showed the female pelvis at birth to be the larger.

Change in the general form of the abdomen was shown to be almost negligible in this period of growth between the 28 mm. crown-heel stage and the 590 mm. crown-heel. A series of diagrams laid out according to the actual measurements show progressive increase in size. These diagrams when reduced to a common scale and superimposed, show only a slight narrowing of the transverse diameter and an appreciable widening of the costal angle. The position of the umbilicus has shifted upward but not to any marked degree. The similarity of contour has been further emphasized by including a series of outlines of casts made direct from the specimens. These outlines of a group ranging from 49 mm. crown-heel length to newborn fit one within the other and the outlines are obviously similar. This investigation shows therefore that the form of the abdomen and its rate of growth must be fixed at an earlier stage than that of any of the specimens included in this series, the smallest of which was 28 mm. in crown-heel length, and that this form and rate is maintained throughout intra-uterine development.

STUDIES ON THE ANATOMY OF THE HUMAN FETAL PELVIS*

FRED L. ADAIR

I. THE OSSIFICATION CENTERS OF THE FETAL PELVIS

The ossification centers of the fetal pelvis were studied by means of transparent specimens, x-ray plates, and the microscopic examination of serial sections.

Thirty-five transparent specimens were prepared by the Schultze method and preserved in glycerin. The complete classification of the material according to sex could not be made. The iliac center is present on the sixtieth day, the first median sacral center on the seventy-eighth day, and the centers of the second and third sacral vertebrae appear shortly after this. The lateral sacral centers appear soon after the median centers of the corresponding vertebrae. The ischial center appears about the ninety-fourth day and the pubic center about the one hundred twenty-ninth day. In the oldest specimen of the series, one hundred forty-eight days, the iliac, four median sacral, probably four lateral sacral, ischial, and pubic centers were all present.

Eighteen specimens were studied by means of the x-ray. Four of the plates were unsatisfactory, leaving fourteen for consideration. The youngest specimen in the series was about eighty-two days. The ischial center appears about the ninety-eighth day when the four median and lateral sacral centers are already present. The pubic center was not demonstrable in this series.

Twenty-five specimens were examined microscopically in serial section. The iliac center appears about the sixty-fifth day, being the first pelvic center to appear; the median centers of the first two sacral vertebrae appear about the seventy-ninth day, the lateral centers of these vertebrae about the one hundred twenty-eighth day, the ischial centers about the one hundred eleventh day, and the pubic centers about the one hundred forty-first day. The centers present on the one hundred sixty-eighth day are the iliac, ischial, pubic, and the four median and lateral sacral centers. The study of the combined series, seventy-four specimens in all, led to the following conclusions:

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Part I is published in full in the American Journal of Obstetrics, 1918, lxxviii, 175–199.

The iliac center is the first to appear in the female pelvis, from about the sixtieth to the sixty-fifth day of fetal life. The median center of the first sacral vertebrae appears next, from about the seventy-fourth to seventy-sixth day. This is followed by the appearance of other median and lateral sacral centers in embryos eighty-two days old. The ischial center appears from about the ninety-fourth to the ninety-eighth day. The pubic center is present on the one hundred twenty-ninth day at which time all other centers which appear until just prior or subsequent to birth are usually present. Practically all antenatal pelvic ossification centers are evident by the end of the nineteenth week of fetal life.

II. RECONSTRUCTION OF THE FETAL PELVIS OF A HUMAN FEMALE

A study was made of serial sections of the pelvic region of a three and one-half months' fetus. Exact scale drawings of the gross specimen were made and microscopic drawings with a magnification of 20 by means of an Edinger projection apparatus. Tracings of these drawings were made on wax plates which subsequently were cut out and assembled into a complete model of the structures in the pelvic region. A description of the structures is given in detail.

PELVIC TUMORS IN CHILDREN*

JOSEPH P. WEYRENS

The rarity of pelvic tumors in children is demonstrated by the fact that of 234,445 patients registered at the Mayo Clinic during the five-year period from January 1915 to January 1920 only eleven were children operated on for this condition. The cases fall into five groups: (1) ovarian tumors, four, (2) tumors of the urinary bladder, two, (3) retroperitoneal tumors, three, (4) intestinal tumors, one, and (5)pelvic abscesses, one.

The conclusions from this study are based on the findings in the eleven cases of pelvic tumors in children reported in the records of the Mayo Clinic and in the evidence in the literature. Benign tumors in children are practically always curable, except those in the bladder which usually result fatally, both in the malignant and benign types. Hematuria is not of much value as a diagnostic sign in this group, as it is rarely present. Frequency and dysuria, however, are very common and may be considered the leading symptoms. Malignant ovarian tumors in children practically always recur after operation, although the immediate surgical risk is small.

Retroperitoneal tumors with evidence of malignancy have a very grave prognosis. It is almost impossible to remove the neoplasm thoroughly enough to prevent recurrence. In cases of benign retroperitoneal tumors the outlook for permanent cure is very good.

Pelvic tumors which are intestinal in origin are good risks from a surgical standpoint, especially if they can be removed directly through the rectum. Tumors of the prostate are practically always sarcomatous and invariably result fatally.

The literature shows the greater number of tumors of the uterus and vagina to be malignant. All patients with malignant disease of the uterus died, while a small percentage of those with malignant tumors of the vagina apparently recovered following operation.

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* Abstract of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery, 1920.

OBSERVATIONS ON THE MUSCULAR SYSTEM OF THE NEWBORN INFANT, WITH SPECIAL REFERENCE TO THE OSSEOUS ATTACHMENTS*

JOHN C. McKINLEY

The chief peculiarities determined by this study of the musculature of the infant, based on the dissection of four specimens, may be summarized by regions as follows:

Head.—The individual muscles of the face of the newborn are like those of the adult; the group as a whole, however, is much reduced, conforming to the relatively small size of the infant face. The small size of the temporal muscles and the shortness of the masseter are very apparent in the newborn.

The cranial attachments of the obliquus capitis superior, rectus capitis posterior major, and the rectus capitis posterior minor of the newborn are all situated more anteriorly than is usual in the adult; those of the semispinalis capitis and trapezius more anteromedially, and those of the splenius capitis and sternomastoid, more medially. The obliquus capitis superior, the rectus capitis posterior major, and the rectus capitis posterior minor attach to the exoccipital portion of the occipital bone in the newborn, whereas in the adult they attach to the linea nuchae inferioris or the nuchal plane immediately below this line (corresponding to the supra-occipital bone of the infant), totally different bones.

Shoulder girdle and upper extremity. Certain muscles attaching to the borders of the scapula extend around to attach to the posterior or anterior side of the border as the case may be. Thus, the upper and lower ends of the insertion of the serratus anterior attach to the posterior surface of the vertebral border; the subscapularis extends on the posterior surface of the lateral margin; the two rhomboidei curve around the vertebral margin to attach to its costal side; and the levator scapulae takes part of its attachment on the costal side of the margin into which it inserts.

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This thesis is to be published in the American Journal of Anatomy.

Muscles in the newborn attached more proximally or not extending so far distally on the humerus as in the adult are the teres major, latissimus dorsi, triceps (lateral head), deltoid, brachialis, coracobrachialis, and pronator teres. The following humeral attachments are either shorter or cover a relatively smaller area: teres major, latissimus dorsi, triceps (lateral head), supraspinatus, brachiaradialis and coracobrachialis. The infraspinatus and subscapularis attachments are relatively longer and narrower than in the adult.

The radial attachment of the extensor pollicis brevis is situated more distally and covers a smaller area in the newborn than in the adult; that of the pronator quadratus is considerably larger, relatively.

The attachments of the brachialis and abductor pollicis longus are more proximal on the ulna in the newborn than in the adult; that of the pronator teres more distal; and that of the flexor carpi ulnaris extends farther distally. The attachments of the triceps, the pronator quadratus and the extensor indicis proprius are relatively more extensive. The insertion of the brachialis is wider but shorter.

Thorax and abdominal wall.—The origin of the subclavius on the first rib does not extend on the costal cartilage. The insertion of the scalenus medius is relatively smaller in the newborn than in the adult while the origin of the sternomastoid on the manubrium is relatively larger and more triangular.

Pelvic girdle and lower extremity.—The origin of the iliacus on the os coxae in the newborn is more extensive over and on the pectineal line than in the adult. The coccygeal attachment of the gluteus maximus is less extensive inferiorly. The piriformis extends farther medially on the inner side of the sacrum. The area of origin of the quadratus femoris is more anterior. The pelvic attachments of the coccygeus, iliacus, gluteus medius, piriformis, obturator internus, ischiocavernosus, and rectus abdominis are all relatively larger; those of the gluteus maximus (sacrococcygeal portion), gluteus minimus, adductor longus and minimus, semimembranosus, and levator ani are relatively smaller. The origin of the glutaeus medius is much broader anteriorly, and correspondingly that of the glutaeus minimus is much reduced.

The adductor brevis is situated more distally and the adductor magnus does not extend so far proximally on the femur in the newborn as in the adult. The femoral attachments of the quadratus femoris, gastrocnemius (medial head), and articularis genu are larger than in the adult.

The tibial attachment of the sartorius extends farther distally; that of the popliteus is less extensive distally; that of the tibialis posterior is more extensive proximally and distally. The peroneus longus has a tibial attachment not described for the adult.

The peroneus brevis extends farther distally; the soleus farther proximally on the fibula than in the adult. The tibialis anterior has a fibular attachment not described for the adult.

Certain of the muscle attachments cross epiphyseal margins and are attached, in part, to the epiphyseal cartilages; in the same connection, certain muscles of the cranium cross the sutures and even the fontanelles. Certain capsular ligaments also cross the neighboring epiphyseal margins, although in most cases of the long bones the capsular ligaments attach wholly to the epiphysis.

In general, the topography of the musculature of the infant is not so unlike that of the adult as might be expected from the differences in bodily proportions at birth and in maturity. In many cases variations from the adult are due to differences in the length, shape, and size of the osseous structures and the size of the underlying viscera, but most of the muscle attachments are similar to those in the adult with the outstanding exception of certain muscles attaching to the skull.

CYSTIC AND FIBROCYSTIC DISEASE OF THE LONG BONES*

HENRY W. MEYERDING

The author's object in this study was to determine if possible, the etiologic factor, clinical course, roentgenographic characteristics, and gross, and microscopic findings which would lead to accurate diagnosis in cases of cystic and fibrocystic disease of the long bones and a conservative method of treatment which would give satisfactory results. The literature was reviewed and available material studied.

The literature, though recent, is of particular interest to the surgeon as it calls attention to a hitherto unrecognized benign lesion. Undoubtedly many of the so-called cures from local excision and amputation for supposed malignant bone tumors were the result of operations for this benign condition. Virchow in 1876 described a cyst of the humerus resulting from liquifaction of chondroma. Rindfleisch in 1886, Hirschberg in 1889, von Recklinghausen in 1891, Back in 1891, and later Muller, Pfeiffer, Bloodgood, Silver, Freiberg, Murphy, Percy, Lotsch and Heineke have written on the subject. The material described was from necropsy findings until 1903 when Heineke reported the use of the roentgen-ray for the first time.

The etiology of fibrocystic disease is obscure; trauma is the most generally accepted factor although many recent authors believe a low grade infection to be the cause but they are unable to demonstrate an organism. In the author's series organisms were found in two cases. All the cases were not subjected to culture. Although the material studied was not extensive enough from which to draw definite conclusions it did not seem probable that the general fibrocystic types could result from trauma. Infection of low grade or a general metabolic disturbance appeared to be a more plausible hypophysis. The author suggests that material should be obtained at operation and carefully studied and cultured. Inasmuch as a like condition is found in Paget's disease and osteomalacia at least the generalized type of fibrocystic disease as described by von Reckinghausen would appear to be due to a disturbance of metabolism, and the metabolic rate and studies of these patients should be obtained.

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TYPES OF CYSTIC DISEASE

Cystic degeneration of enchondroma, single or multiple (Virchow).
Callous, subperiosteal, hemorrhagic, resulting from trauma
Cyst occurring in osteomalacia.
Cyst occurring in osteitis deformans (Paget's).
Localized osteitis fibrosa cystica
General osteitis fibrosa cystica (von Recklinghausen).
Echinococcus and cysticercus cysts.
Dentigerous.
Cysts occurring from mercurial poisoning
Cysts resulting from infection.

Symptoms vary, and in some instances a fracture is the first indication of the disease in the bone. Usually, however, there is rheumatic or neuralgic pain, and a local swelling or thickness in the bone. In some instances, tenderness, atrophy, deformity, shortening, or a limp is complained of. The disease usually appears before thirty years of age and practically always in the diaphysis; it seldom or never invades the epiphysis. There is no thickening in the periosteum nor tendency to burst through the periosteum into the soft tissues as frequently occurs in malignant diseases. If the cyst becomes multilocular it presents a series of translucent areas surrounded by striæ or irregular outline, known as trabeculations. The cortex, gradually encroached on, becomes thin or fused with the medullary substance so that there are areas in which only the outline of the cortex can be made out. Later the bone, having lost its normal structure, becomes weak and fractures on moderate trauma.

The diagnosis can be made only from a thorough clinical history, physical examination, and roentgenographic examination, and then cannot always be determined with certainty until an exploratory operation and pathologic examination. The principal points to be determined are the question of malignancy, the site and extent of bone involvement, and whether the disease is truly a local process. The roentgenogram is one of the greatest aids in determining this, and especially in distinguishing between single and multiple types, and in determining the probable extent of operation. In all cases of fibrocystic disease, roentgen-ray examination of all long bones is advisable.

Nineteen cases are reported, with the histories, and roentgenographic and microscopic findings. Differential diagnosis is made between giant-cell tumor, carcinoma syphilis, and osteomyelitis. Conservative surgery was advised: thorough removal of the diseased area and crushing in of the thinned cortex and closure without drainage.

CONCLUSIONS

1. Cysts and osteitis fibrosa cystica may arise from other local or general processes.

2. Cysts, osteitis fibrosa cystica, and giant cells may occur in the same bone.

3. Giant cells in moderate numbers, especially the atypical forms, are not prognostic of malignancy.

4. Before diagnosis of a local osteitis fibrosa cystica is made, it is necessary to rule out the general form; this is most practical by means of the roentgenograph.

5. Curetting and crushing in of the diseased wall is usually sufficient surgery.

6. The microscopic picture is clear and should not be confounded with malignancy.

7. The roentgenograph is of the greatest value and it is fairly diagnostic, but it cannot accurately determine the contents of the cyst; the localization in the diaphysis and the tendency to remain inside the cortex and periosteum are valuable signs in the differentiation from maligancy, the epiphysis being free from involvement.

8. The history, clinical findings, examination of the patient, and laboratory and roentgenographic reports should be included in making the diagnosis.

IX

METABOLISM

CLINICAL METABOLISM*

IRENE SANDIFORD

PART I. TECHNIC OF BASAL METABOLIC RATE DETERMINATIONS FOR CLINICAL PURPOSES

The technic of determining the basal metabolic rate at the Mayo Clinic is described in full.

PART II. THE EFFECT OF THE SUBCUTANEOUS INJECTION OF ADRENALIN CHLORID ON THE HEAT PRODUCTION, BLOOD PRESSURE, AND PULSE RATE IN MAN

The results of forty-six experiments on the effect of the subcutaneous injection of adrenalin chlorid (0.5 c.c. of 1:1000) on the metabolic rate, respiratory quotient, pulse rate, and blood pressure, are reported. These studies were made chiefly on groups of patients who showed variations in the activity of the thyroid, pituitary or adrenal glands, as well as on a small group of clinically normal controls. The results are in agreement with those obtained by Tompkins, Sturgis and Wearn.

Adrenalin invariably caused an increase in the heat production, and in thirty-nine experiments there was an increase in the respiratory quotient. This rise in heat production was usually accompanied by an increase in the ventilation rate, as a rule in the respiration rate, in the number of heart beats each minute, volume of each beat, and greater utilization of the blood-carrying power and peripheral vascular dilatation with an increased systolic and decreased diastolic blood pressure. Not all these compensatory factors necessarily come into play in each instance. As would be expected, various combinations may occur, sometimes one factor, sometimes another factor acting as the major compensation. The data show that there is no relationship between the character of the adrenalin reaction and the degree of activity of the thyroid gland, and the opinion is therefore expressed, contrary to that of Goetsch, that the reaction is not indicative of the presence or absence of hyperthyroidism.

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* Abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1919.

Part I is incorporated in a laboratory manual published by Boothby, W. M. and Sandiford, Irene: Basal metabolic rate determinations. Philadelphia, Saunders, 1920, 115 pp.

Part II is published in full in Endocrinology, 1920, iv, 71–87.

Part III is published in full in the American Journal of Physiology, 1920, li, 407–422.

The similarity of the metabolic rate curve following the injection of adrenalin chlorid to that found by Lusk from a carbohydrate plethora naturally directs attention to the possibility that the increased heat production is due to an excess of carbohydrate metabolites. There may be, however, in addition a direct chemical stimulation of cellular combustion.

PART III. THE BASAL METABOLIC RATE IN CASES OF EXOPHTHALMIC GOITER OBSERVED DURING 1917, WITH A BRIEF DESCRIPTION OF THE TECHNIC USED AT THE MAYO CLINIC

The clinical value of determinations of the basal metabolic rate in disorders of the thyroid gland is illustrated by a report of the results obtained in the cases of exophthalmic goiter observed during 1917 before and after treatment. In thirteen cases there was a decrease in the basal metabolic rate from an average of +59 per cent to +46 per cent after approximately one week's rest in bed. A single ligation in sixteen cases caused a drop in the metabolic rate from +54 per cent to +44 per cent. The effect of a primary thyroidectomy in nineteen cases was a drop in the metabolic rate from +31 per cent to +5 per cent. The general effect of the treatment adopted at the Mayo Clinic for severe cases of exophthalmic goiter may be illustrated by the following data:

In a group of twenty-two cases the average metabolic rate before any treatment was instituted was +66 per cent. As a result of rest in bed and two ligations the rate before the patient went home had decreased to +46 per cent. The further improvement that occurred from three months' rest at home reduced the average metabolic rate to +39 per cent, and finally, after thyroidectomy, and just before the patients were discharged from the Clinic, the rate was +16 per cent. The basal metabolic rate is considered the only accurate index to the degree of hyperthyroidism and of the effect of either medical or surgical treatment of such cases.

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STUDIES IN THE NITROGEN METABOLISM OF BACTERIA*

ANNE G. BENTON

The experiments here recorded were undertaken with the idea of gaining some information, if possible, concerning the materials which usually serve as a source of nitrogen to bacteria, the actual form in which the nitrogenous substances are absorbed, and whether all simple dialyzable protein decomposition products are of equal usefulness in building up the cell substance.

The bulk of investigations of proteolysis in the past has had to do with the identification or determination of end-products. The early researches using mixed cultures on putrescible materials, although not usually controlled as to the exact chemical constituents of the medium, or the strains of bacteria employed, showed that the formation of certain substances such as ammonia, hydrogen sulphid, skatol, and so forth is characteristic of putrefaction irrespective of the precise nature of the protein or the particular varieties of organisms present. Productive of much more knowledge of actual bacterial metabolism was the long list of researches using pure cultures and mediums of known composition, making tests to determine the nature of the compounds formed. The indol test is the best known and most useful result of the investigations carried out on peptones or other tryptophane-containing medium.

Herter and Broeck using a 1 per cent preparation of casein with *Bacillus proteus* demonstrated the presence of primary amins, hydrogen sulphid, fatty acids, aromatic oxyacids, indol, and indol acetic acid. Nawiasky compared the products used up by *Bacillus proteus* on a medium rich in peptone with those assimilated by Vibrio Finkler, *Bacillus fecalis-alkaligenes*, and *Bacillus mesentericus*, and states that *Bacillus proteus* attacks albuminoses much more actively than do the others, but that its action on peptones and creatin was less marked. Rettger planted *Bacillus putrificus* Bienstock, *Bacillus edematis maligni*, *Bacillus anthracis-symptomatici*, *Bacillus coli*, and *Bacillus lactis-aerogenes* on special egg-meat medium and tested for indol, skatol, phenol, aromatic oxyacids, skatol-carbonic acid, tyrosin, leucin, albumoses, peptones, tryptophane, hydrogen sulfid, and mercaptan, his conclusion being that only the obligate anaerobes cause true putrefaction. Later with Newell he tried twenty-six strains of Bacillus proteus on egg-meat medium, blood fibrin suspended in broth, and Uschinsky's medium and concluded that, while actively proteolytic, Bacillus proteus does not form those end-products characteristic of putrefaction in the narrow sense of the word. Effront studied *Bacillus proteus*, *Bacillus sporogenes*, *Bacillus mesentericus*, *Bacillus butyricus*, *Bacillus putrificus* Bienstock, and so forth, in a similar manner on albuminoid mediums. Sasaki's researches on the particular substances formed from glycyl-glycin, glycyl tyrosin, cystin and tyrosin are of interest and value as pictures of a certain stage of protein degradation, as are the works of Braasch on glutamic acid, serin, and tyrosin.

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The bibliography is herewith omitted.

While investigations like those mentioned are of diagnostic importance, and throw much light on the types of chemical activity of which a given bacterium is capable, a definite idea of the metabolism of an organism cannot be obtained from purely qualitative data or from a single quantitative determination of some particular product. For such purposes a series of quantitative determinations should be made on a favorable medium, under conditions of vigorous normal growth. Many factors enter into the nature and amount of decomposition products formed: first, the availability of the nitrogenous compounds present, depending on whether or not the organism in question is capable of elaborating a ferment to digest them, the molecular point of attack of the enzyme, whether intermediate products are present, and, if so, what and in what quantity, what proportion of the split molecules are resynthesized into bacterial protein and which are left in the medium, and whether or not some of the compounds present are assimilated in preference to others. In the case of any particular end-product it is desirable to know whether it represents a portion of the protein molecule unattacked by the bacteria, a true cell excretion, or something set free by the death of the cell or by autolysis. Any systematic investigation of the proteolytic activity of an organism should include at least the following points:

1. Determination of the amounts present of certain available food substances.

2. Periodic determination of the amounts of one or more decomposition products used as a measure of proteolysis.

3. Allowances for such factors as rate of increase in numbers, presence of other non-nitrogenous foodstuffs, presence of decomposition products toxic to the cells of inhibitory of their activity, and products of autolysis of dead cells.

The infinite complexity of proteins, their delicate susceptibility to change under the influence of chemical and physical agents used for their isolation and purification, and the purely technical difficulties involved in an attempt to avoid accidental contaminations while preserving optimum conditions of growth as well as the refinements of chemical technic necessary to quantitative determination, have tended to discourage this type of research, with the result that there are comparatively few such studies on record, all more or less incomplete.

Among the end-products of putrefaction which have been determined quantitatively as a measure of proteolysis, ammonia has been the most common. Effront made use of it in his studies on yeast. Emmerling and Reiser stated that at least 25 per cent of the nitrogen in gelatin was converted into ammonia by *Bacillus fluorescens-liquefaciens*, while Arnaud and Charrin found that in three days *Bacillus pyocyaneus* converted 91 per cent of the nitrogen in asparagin into ammonia and that a three weeks' culture in gelatin contained ammonia to the amount of 70 per cent of the total nitrogen. Boencke, and Kendall and Farmer determined ammonia to check the degree of proteolysis in their studies on the protein-sparing influence of carbohydrate. While the information thus obtained is valuable, particularly in the case of the putrefactive saprophytes, the ammonia curve admits of varying interpretations unless checked by other determinations. Moreover, many pathogens do not liberate much ammonia during their short period of life in artificial cultures (Berghaus). The quantitative determination of indol and of phenol, valuable as they are in the study of *Bacillus coli* and similar organisms, has the same limitation.

At the other extreme of the metabolic process, the progress of proteolysis may be observed by systematic determinations of the amount of coagulable protein remaining in the culture medium. De Waele and Vendevelde worked out these results with a variety of organisms planted on gelatin, milk, and casein broth in an endeavor to settle the question of the specificity of bacterial proteases. Bainbridge, Rettger and Sperry working with representative pathogenic and saprophytic strains on medium composed of mineral salts and pure protein (crystallized egg albumin, serum protein, alkali albumin, and edestin) have proved that such growth as may occur on solutions of unchanged proteins is due to the minute amounts of nitrogenous impurities present, and that in the absence of split-protein products the germs are unable to attack native albumin.

The quantitative determination of amino-acids is particularly useful, especially if checked by comparison with the amount of destruction of the protein or split-protein which is their source, or, in experiments using the amino-acids as a source of nitrogenous food, estimations of the ammonia which is their fate (Nawiasky). Until very recently Sorensen's formol-titration method has been the most in use. This procedure was followed by Rosenthal and Patai who planted virulent and avirulent strains of staphylococcus, streptococcus and *Bacillus coli* on broth. With all three of these organisms they observed an initial sharp rise of amino-acid, followed by a more gradual rate of increase. Meserintsky observed a progressive augmentation of the amount of amino-acid present in a 10 per cent gelatin culture of Bacillus prodigiosus, which, however, represented only a portion of the non-coagulable nitrogenous material present. Frouin and Ledebt, working with *Bacillus coli*, *Bacillus typhosus*, *Bacillus dysenteriae* and *Bacillus cholerae* on a solution of non-nitrogenous mineral salts enriched with amino-acids were unable to detect any decrease during the first 24 hours of growth, though the diminution became apparent later. Kendall, Day and Walker attempted to use Sorensen technic in addition to determinations of ammonia, total nitrogen and acidity in their work on the protein-sparing action of glucose, but abandoned the amino-acid estimation because "the results furnished no information of importance."

The more delicate and accurate method of Van Slyke now makes it possible to obtain much more significant estimation of the progress of proteolysis, since the micro-apparatus is accurate to 0.005 mg. of nitrogen.

This method was used by Sears on peptone, broth, and gelatin cultures of a great variety of organisms. He also determined ammonia and creatinin. While some of his cultures showed a gradual increase in amino-nitrogen, the majority exhibited fluctuating rises and falls indicating in his opinion that amino-acids were formed and broken continuously during the life of the culture.

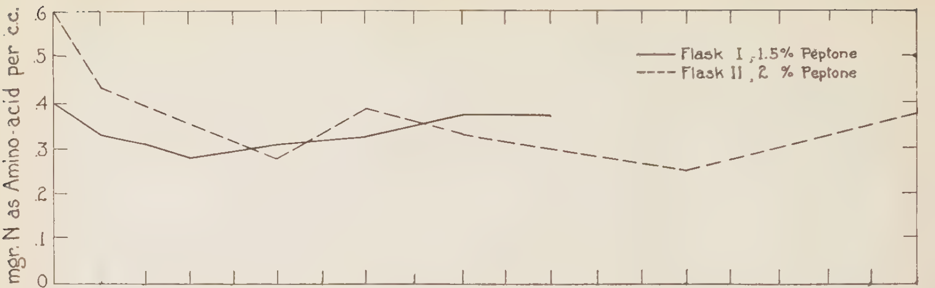
To arrive at a more nearly complete understanding of the nitrogen metabolism of bacteria it would seem valuable not only to apply such a series of tests to growth on peptone-containing mediums, but also to study the amino-acid content of cultures on some material which contains native albumin. This is particularly true of the pathogens, many of which do not thrive on plain peptone or broth. Moreover, their behavior in a medium closely resembling blood-serum or some other body fluid is well worth detailed consideration, both for the insight it might give into the process of infection, and the possibility of the usefulness of such data in attacking the chemical side of problems of immunity. Ascitic fluid is more similar to blood serum than any other material which can easily be obtained sterile in sufficient quantity for such purposes. Accordingly, determinations have been made on *Bacillus typhosus*, *Bacillus proteus*, *Bacillus pyocyaneus*, and staphylococcus grown on broth, on pure ascitic fluid, and on mixtures of equal quantities of the two. In order to rule out the protein-sparing properties of carbohydrates as much as possible in the interests of simplicity, sugar-free broth was used. Such broth may contain considerable amounts of amino-acid determined by Van Slyke's method in addition to the peptones, but no coagulable albumin or carbohydrates. In ascitic fluid, on the other hand, the amount of amino-acid and other protein decomposition products is small, while the nitrogen present as coagulable protein is considerable. A small amount of carbohydrate is probably present, but no tests for it were made. A mixture of equal parts of broth and ascitic fluid represents a middle ground between these conditions. In the experiments recorded in Tables 4 and 10 ascitic fluid was distributed in equal amounts (10 c.c.) in a series of sterile test tubes, and each inoculated with a loopful of broth culture. At regular intervals the amino-acid content of one tube was determined, the loss by evaporation being carefully made up with distilled water. While this method has the advantage of permitting determinations to be made without danger of contamination of the material destined for later analysis, there is always the possibility of a considerable variation in the seeding of the different tubes or even in the samples of ascitic fluid. The rest of the work was done with flasks containing a quarter of a liter or more of the medium. Tight fitting rubber caps over the cotton stoppers protected against evaporation. At intervals samples were removed with sterile pipettes after shaking the flask to render the medium homogeneous. These were centrifuged and the supernatant liquid (practically, though probably not absolutely, free of bacterial cells) was tested for the amount of amino-acid present, and in some cases for coagulable protein. In cases where numbers of bacteria present are given, they were determined by counting agar plates made with the customary quantitative precautions. The Kjeldahl determinations were run in duplicate, and the results averaged if they did not check but showed a difference of less than 0.5 c.c. in the titration. Figures showing a wide variation were discarded. Two Van Slyke determinations were made routinely, checked by a third in case the amounts of nitrogen liberated did not agree within 0.03 c.c.

Table 1.—Staphylococcus

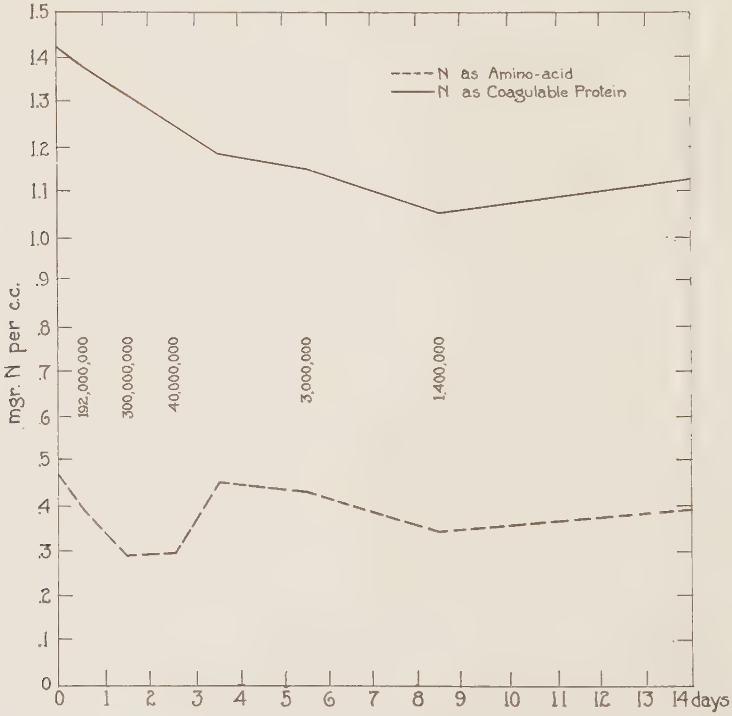
Milligrams N as amino-acid per c.c. in broth

Incubation	Flask 1 (2 per cent peptone)	Flask 2 (1.5 per cent peptone,
Sterile	0.606	0.407
1 day	0.438	0.333
2 days		0.315
3 days		0.280
5 days	0.280	0.319
7 days	0.390	0.328
9 days	0.332	0.376
11 days		0.369
14 days	0.252	
19 days	0.380	

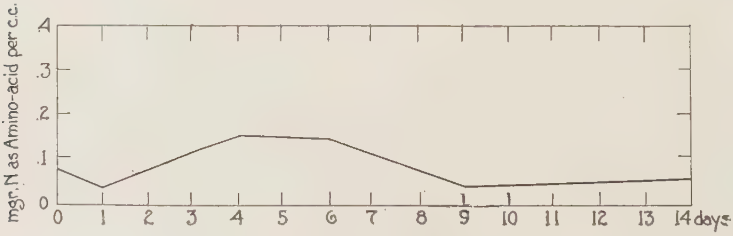
The staphylococcus cultures on broth (Table 1, Fig. 194*a*) show a drop to 0.29 mg. though Flask 1 originally contained nearly half again as much amino-acid as Flask 2. Flask 1 is shown as having reached this minimum two days later than Flask 2 but this may well be due to the fact that no three-day determination was recorded. In Flask 2 there was a steady gradual rise after reaching the minimum until the point when it had to be discarded on account of contamination.



a. On Sugar-free Broth.



b. On Sugar-free Broth + Ascitic Fluid.



c. On Pure Ascitic Fluid

FIG. 194.—Staphylococcus.

Flask 1 shows fluctuations which are without significance when not checked by determinations of other substances.

On a mixture of borth and ascitic fluid (Table 2 and Fig. 194*b*) the amino-acid curve shows a decided fall during the period of most rapid multiplication, followed by a rise and later some fluctuation.

TABLE 2.—STAPHYLOCOCCUS

Milligrams N per c.c. as amino-acid and as coagulable protein in a mixture of ascitic fluid and broth

Incubation	Amino-acid	Coagulable protein	Bacteria per c.c.
Sterile............	0.468	1.420	
12 hours..........	0.393	1.382	192,000,000
36 hours..........	0.295	1.312	300,000,000
60 hours..........	0.306		40,000,000
84 hours..........	0.445	1.189	
132 hours..........	0.425	1.158	3,000,000
8½ days...........	0.341	1.052	1,400,000
14 days...........	0.390	1.134	

On pure ascitic fluid (Table 3, Fig. 194*c*) although the amount of amino-acid present to begin with was much smaller than in any of the other flasks, we observe the same initial drop followed by a slight rise and a subsequent fall.

TABLE 3.—STAPHYLOCOCCUS

Milligrams N as amino-acid per c.c. of pure ascitic fluid

Incubation..........	Sterile	1 day	3 days	4 days	6 days	9 days	14 days
Milligrams N.........	0.067	0.033	0.112	0.145	0.143	0.033	0.054

Apparently this organism readily assimilates a part at least of the amino-acids found in each of these mediums but attacks the coagulable protein to some extent from the first. After about three days there comes a period when amino-acids accumulate, apparently due partly to autolysis and partly to the fact that the original content of assimilable amino-acid is exhausted, and only a portion of those liberated from the proteins, peptones, and so forth, can be used by the organism. The increase of coagulable protein after the eighth day may be due to the fact that, as the cultures grew older, it became increasingly difficult to get a clear supernatant fluid by centrifugation.

The results obtained in similar mediums with *Bacillus pyocyaneus* are noticeably different. On pure ascitic fluid (Table 4, Fig. 195*c*), after an initial drop, a steady rapid rise in amino-acid is observed.

Table 4.—Bacillus Pyocyaneus

Milligrams N as amino-acid per c.c. of ascitic fluid

Incubation	Sterile	1 day	2 days	3 days	5 days	8 days	10 days	12 days
Milligrams N	0.077	0.049	0.013	0.074	0.099	0.249	0.493	0.695

On sugar-free broth, however, there is a variation (Table 5, Fig. 195*a*) which may be significant. After the original drop (which would perhaps be more noticeable if a two-day determination had been made) and a subsequent increase between the thrid and sixth days, there is an unmistakable drop shown on the eleventh day. Apparently, after exhausting the favorite amino-acids present in the peptone, the organism attacks the previously unused amino-acid while in an abundance of available protein it continues uneconomically to select for synthesis the molecules best adapted to its needs.

Table 5.—Bacillus Pyocyaneus

Milligrams N as amino-acid per c.c. of broth

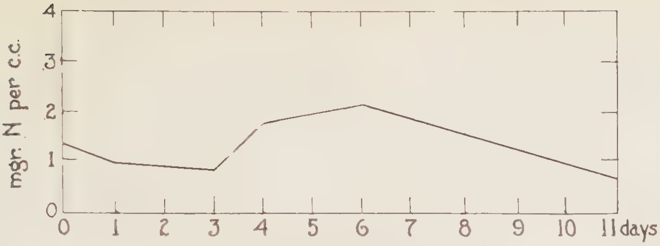
Incubation	Sterile	1 day	3 days	4 days	6 days	11 days
Milligrams N	0.1384	0.098	0.086	0.184	0.215	0.066

On a mixture of broth and ascitic fluid (Table 6, Fig. 195*b*) the results are somewhat similar, except that the rise in amino-acid occurred earlier. Here, too, we have a decrease in amino-nitrogen after the fourth day, although there is destruction of protein going on at the

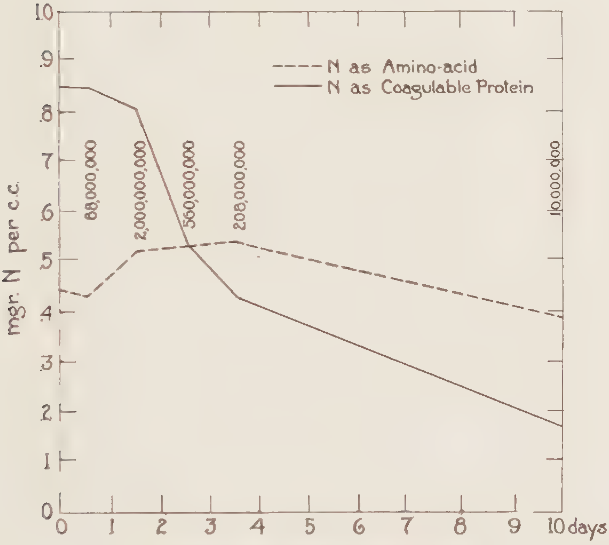
Table 6.—Bacillus Pyocyaneus

Milligrams N per c.c. as amino-acid and as coagulable protein on ascitic fluid + sugar-free broth

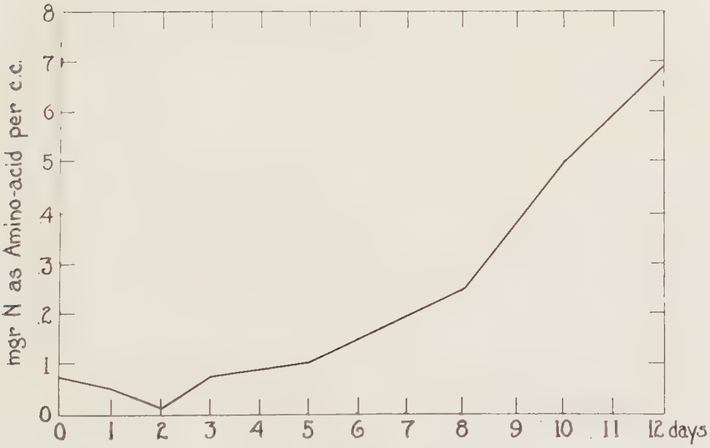
Incubation	Amino-acid	Coagulable protein	Bacteria per c.c.
Sterile	0.441	0.846	
12 hours	0.439	0.846	88,000,000
36 hours	0.520	0.818	2,000,000,000
60 hours	....	0.529	560,000,000
84 hours	0.537	0.433	208,000,000
10 days	0.386	0.172	10,000,000



a. On Sugar-free Broth.



b. On Sugar-free Broth + Ascitic Fluid.



c. On Pure Ascitic Fluid.

FIG. 195.—Bacillus Pyocyaneus.

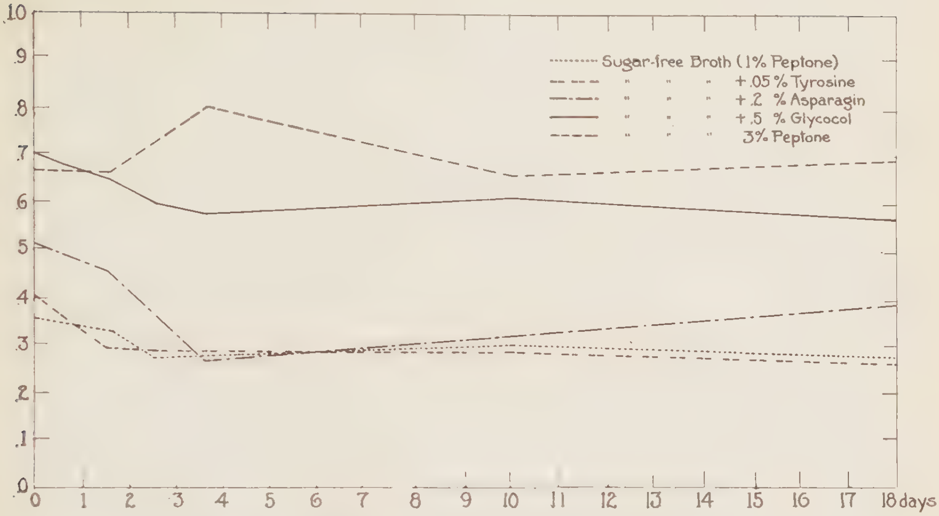
same time. Curiously enough, the greatest destruction of protein took place after the maximum count had been passed and at a time when the free amino-acids were not noticeably increasing. The protein destruction might be attributed to the activity of the enzymes previously secreted by the bacteria but in that case an increase of amino-acid would be expected. The fact that the acids do not remain free in the culture can be explained on either of two suppositions: that the enzymes secreted were of more than one kind and could carry preteolysis beyond the amino-acid stage or, on the other hand, that cell division and consequently synthesis of amino-acid into bacterial protoplasm was proceeding at a maximum rate during this period, the apparent decrease in numbers being due to the fact that the death rate began to make itself felt at the point when the count was 2,000,000,000.

In order to throw more light on this apparent preference for some protein-decomposition products instead of others, it seemed useful to investigate the effects of the addition of varying amounts and kinds of amino-acids to culture mediums. Accordingly, 0.1 c.c. of forty-eight-hour broth culture of *Bacillus typhosus* was inoculated into each of five flasks of sugar-free broth which differed only in that Flask 1 was ordinary sugar-free broth containing 1 per cent peptone, Flask 2 contained in addition 0.05 per cent tyrosin, Flask 3,0.02 per cent asparagin, Flask 4,0.5 per cent glycocol, and Flask 5, extra peptone making a strength of 3 per cent. The results are given in Table 7 and represented graphically in Figure 196*a*.

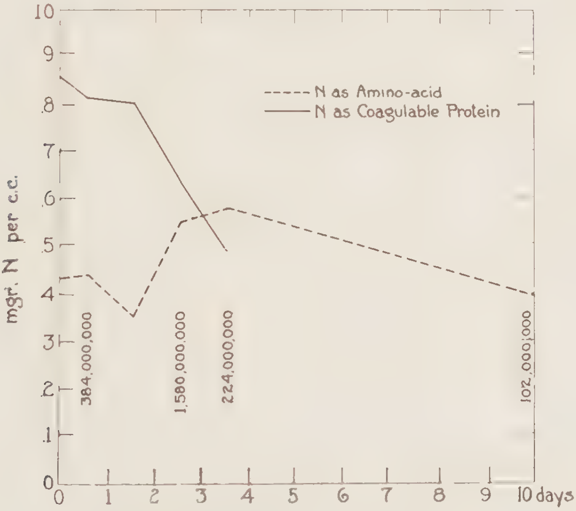
TABLE 7.—BACILLUS TYPHOSUS

Milligrams N as amino-acid per c.c. on broth of varying amino-acid content

Incubation	1 per cent peptone	0.05 per cent tyrosin 1 per cent peptone	0.2 per cent asparagin 1 per cent peptone	0.5 per cent glycocol 1 per cent peptone	3 per cent peptone
Sterile..........	0.357	0.401	0.520	0.715	0.678
16 hours........		0.343			
18 hours........				0.686	
36 hours........	0.321	0.295			
38 hours........			0.452	0.651	0.667
60 hours........	0.277	0.282		0.605	
90 hours........			0.272	0.577	0.806
10 days.........	0.309	0.315		0.619	0.663
18 days.........	0.277	0.265	0.389	0.567	0.686



a. On Sugar-free Broths of different Amino-acid Content.



b. On Sugar-free Broth + Ascitic Fluid.

FIG. 196.—Bacillus Typhosus.

In the flask of plain sugar-free broth we note a gradual decrease in amino-acid during the first two days. This period covers the lag-phase and the period of most rapid multiplication, during which it uses those acids present in the medium which the organism is especially able to assimilate. The fact that no great change was apparent at the times when subsequent tests were made would seem to indicate that the peptone in the culture was being used, and that the resulting decomposition products were either synthesized into bacterial protoplasm or else carried beyond the amino-acid stage. However, there seems to be a certain amount of amino-acid present which remains untouched, doubtless being unsuitable as nutriment for the cells. In the tyrosin flask the same level is reached and maintained after sixty hours, indicating that the extra foodstuff in that form was readily assimilated. The flask with asparagin shows the same process in a more striking degree. It is unfortunate that no sixty-hour test was made to determine whether the asparagin was used up in that length of time, or really required three and one-half days to reach the dead level as the chart seems to show. The flask which contained a considerable amount of glycocol shows a similar absolute decrease, but the level maintained is higher than that of the other flasks by just about the amount of glycocol added. (The difference in amino-acid nitrogen between the plain broth flask and the one with glycocol was 0.358 mg. for each c.c. when sterile, and 0.354 mg. after ten days' incubation.) This apparently indicates that glycocol is not assimilated by *Bacillus typhosus* when other sources of nitrogen are present. In the 3 per cent peptone flask there is very little decrease during the first one and one-half days, indicating that the free amino-acid used up is balanced by the fact that some is being set free from the peptone. After this, apparently the peptone destruction sets free more acid than is used up, but later still these are synthesized or more likely broken down into simpler substances. (Sears found that *Bacillus typhosus* formed considerable amounts of ammonia on peptone solution.)

These results are confirmed and explained by an experiment using a medium consisting of mineral salts, glycerol and a pure amino-acid. Absolutely no visible growth of *Bacillus typhosus* could be determined in such a medium with glycocol as a sole source of nitrogen, although it grew well on this medium when other amino-acids were introduced, and several other bacteria produced a heavy growth on the glycocol. In the typhoid-glycocol culture tubes there was no appreciable diminution of the amount of amino-acid present during three weeks, though the bacilli introduced remained viable throughout the period of observation.

The results obtained with the same strain on a mixture of sugar-free broth and ascitic fluid (Table 8, Fig.196*b*) are of interest in connection with the first experiment.

TABLE 8.—BACILLUS TYPHOSUS

Milligrams N per c.c. as amino-acid and as coagulable protein in a mixture of broth and ascitic fluid

Incubation	Amino-acid	Coagulable acid	Bacteria per c.c.
Sterile	0.430	0.859	
12 hours	0.439	0.818	384,000,000
36 hours	0.354	0.805	
60 hours	0.551	0.639	1,580,000,000
84 hours	0.581	0.488	224,000,000
10 days	0.386	Lost	102,000,000

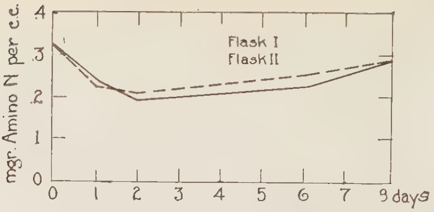
Here the protein is attacked from the first, and there is even a slight rise in amino-acid during the first twelve hours, then a considerable fall in the next twenty-four hours, followed by a rapid rise in free amino-acid, and great destruction of protein continuing even a little after the maximum count was reached. Then ensues a period during which the amino-acids are gradually used up by the germs.

The two flasks of ordinary sugar-free broth inoculated with *Bacillus proteus* (Table 9, Fig. 197*a*) indicate that, after the first drop due to the ultilization of the amino-acids present, very little of the amino-acid broken from the peptone is left free in the medium, and the accumulation is not great.

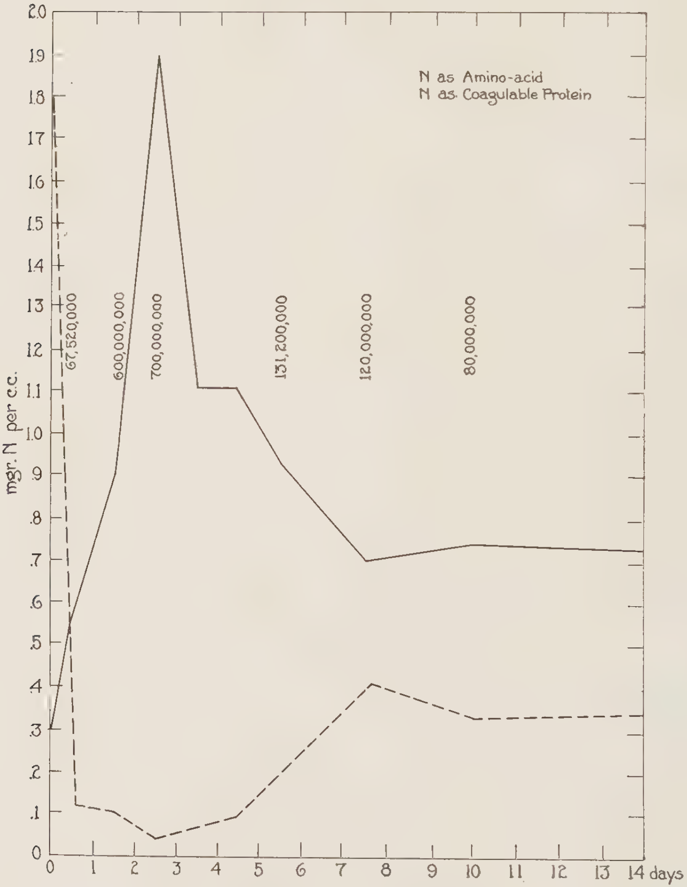
TABLE 9.—BACILLUS PROTEUS

Milligrams N as amino-acid per c.c. of broth

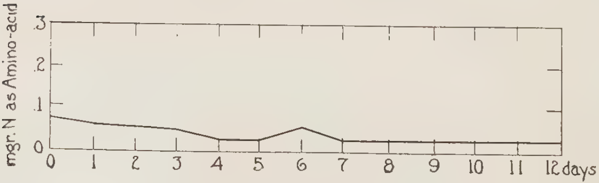
Incubation	Flask 1	Flask 2
Sterile	0.329	0.329
1 day	0.239	0.233
2 days	0.191	0.202
6 days	0.230	0.235
8 days	0.282	0.282



a. On Sugar-free Broth.



b. On Sugar-free Broth + Ascitic Fluid.



c. On Pure Ascitic Fluid.

Fig. 197.—Bacillus Proteus.

On undiluted ascitic fluid (Table 10, Fig. 197*c*) this is even more marked. Unfortunately, determinations of coagulable protein were not made, but the idea that the small amount of free amino-acid is due to thoroughness of decomposition rather than to lack of protein is strengthened by the fact that this was the same sample of fluid on which Bacillus pyocyaneus set free 0.695 mg. for each c.c. in twelve days.

TABLE 10.—BACILLUS PROTEUS

Milligrams N as amino-acid per c.c. pure ascitic fluid

Incubation....	Sterile	1 day	2 days	3 days	4 days	5 days	6 days	7 days	12 days
Milligrams N.	0.077	0.060	0.054	0.043	0.026	0.031	0.054	0.032	0.026

On the mixture of broth and ascitic fluid (Table 11, Fig. 197*b*) the striking destruction of coagulable protein, and the very large amount of amino-acid liberated in the first two and one-half days apparently indicates that this organism attacks both protein and peptones whenever they are present, indiscriminately, and uneconomically in the case of a medium rich in both. Later much of this surplus amino-acid was used up.

TABLE 11.—BACILLUS PROTEUS

Sugar-free broth plus ascitic fluid

Incubation	N per c.c. as NH_2	N per c.c. coagulable protein	Count
Sterile............	0.307	1.807	0
14 hours...........	0.575	0.119	67,520,000
36 hours...........	0.900	0.105	600,000,000
2½ days..........	1.980	0.049	700,000,000
3½ days..........	1.175		
4½ days..........	1.173	0.091	
5½ days..........	0.934	.....	131,200,000
7½ days..........	0.707	0.412	120,000,000
10 days..........	0.743	0.337	80,000,000
2 weeks........	0.732	0.348	

In this flask as in the staphylococcus flask already mentioned, it was almost impossible to obtain a clear fluid by centrifugation after the first week, and this probably accounts for the rise in coagulable protein noted on the seventh day.

It is interesting to compare the results on the flasks of broth reinforced with various amino-acids (Table 12, Fig. 198) with the results on plain broth as well as with the behavior of *Bacillus typhosus.*

TABLE 12.—BACILLUS PROTEUS

Incubation	0.05 per cent tyrosin	0.2 per cent tyrosin	0.2 per cent asparagin	0.5 per cent glycocol	3 per cent peptone
Sterile..........	0.327	0.440	0.469	0.480	0.402
12 hours........	0.345	0.449	0.276	0.556	0.503
36 hours........	0.309	0.292	0.220	0.496	0.499
60 hours........	0.199	0.254	0.165	0.417	0.386
84 hours........	0.209	0.175	0.219	0.602	0.481
4½ days.......	0.188	0.210	0.190	0.485	0.397
5½ days.......	0.212	0.201	0.257	0.491	0.372
7½ days.......	0.199	0.255	0.221	0.518	0.408
10½ days.......			0.219		
11½ days.......	0.209	0.188		0.208	0.297
17 days.......	.....			0.204	
18 days.......	0.209	0.222	0.155		0.255

Here only one flask showed an initial fall in amino nitrogen content, namely, that containing asparagin. This substance is apparently assimilated with considerable vigor at the same time that the peptone is being broken down, and the "dead level" of useless amino-acid is reached in two and one-half days. In the case of tyrosin the amounts set free in excess of the amounts liberated during the first twelve hours but in a few days the content is about the same as that of the asparagin flask. The glycocol flask shows a very different curve from that produced with *Bacillus typhosus.* Here we have an initial rise due to the attack on peptone, followed by fluctuations and a three-day period of no great change, and then a rapid fall between the seventh and eleventh days, when the "dead level" was reached. In the 3 per cent peptone flask the initial increase is more marked than in any of the others, which is what might be expected, considering the readiness of the organism to attack such substances, and the fact that there is three times as much peptone present as in each of the other four flasks.

The results on the synthetic medium (mineral salts, glycerol and a single amino-acid) agree with these findings. While *Bacillus proteus* did not use up glycocol as rapidly as some other bacteria did, it grew fairly well, proving that it can derive nitrogen from this acid if "starved

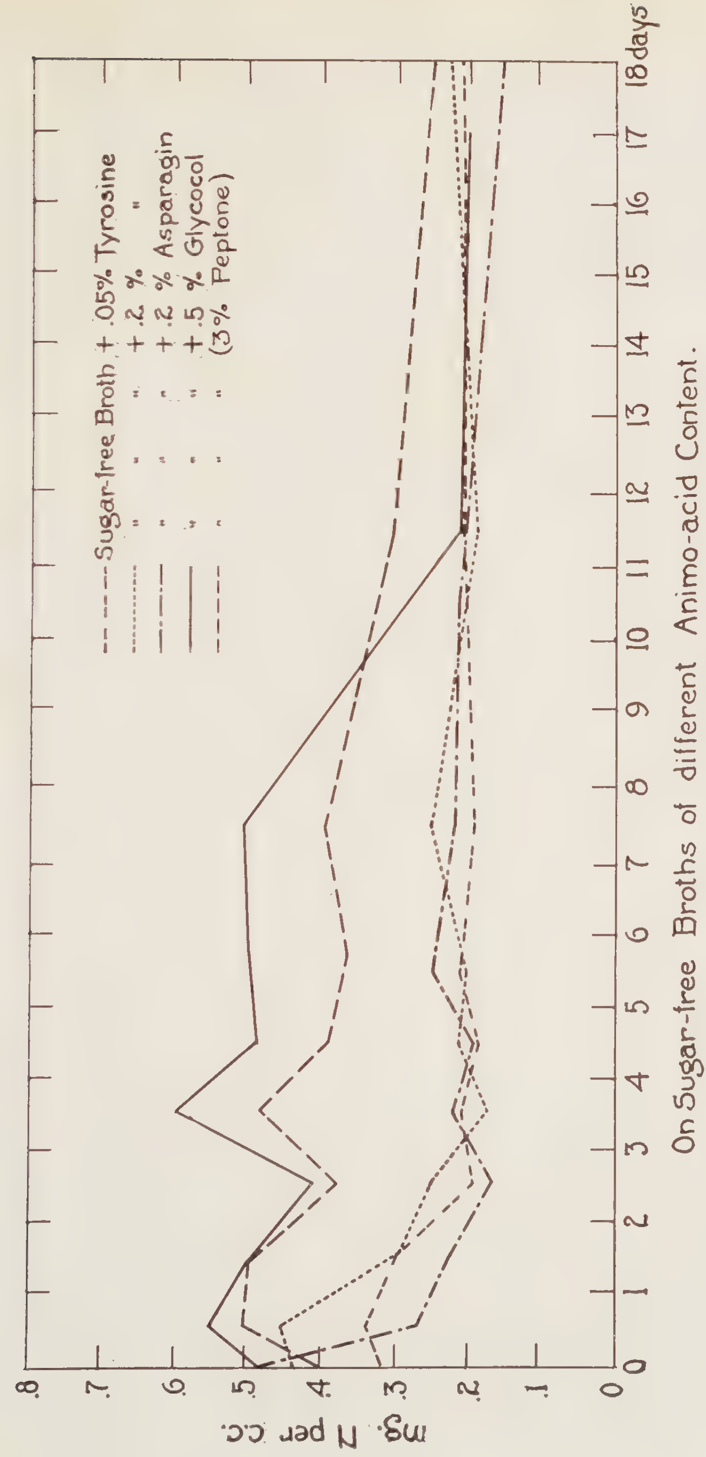


FIG. 198.—Bacillus "Proteus.

to it." These peculiarities seem worthy of further study. It was thought possible that this difference might have some bearing on the liquefaction of gelatin, which yields a large percentage of glycocol on hydrolysis. However, several bacteria (*Bacillus paratyphosus, Bacillus coli, Bacillus fecalis-alkaligenes*) incapable of liquefying ordinary gelatin mediums, thrive on these glycocol solutions. Investigations using a variety of amino-acids for a considerable number of organisms promise interesting results, and are well under way.

SUMMARY

Four organisms were studied, two of which are strongly proteolytic on ordinary mediums (*Bacillus proteus* and *Bacillus pyocyaneus*), one moderately so (staphylococcus), and one (*Bacillus typhosus*) which does not show the marked activity of the others. On mediums containing ascitic fluid all four destroyed considerable amounts of coagulable protein during the first thirty-six hours. *Bacillus pyocyaneus* was the only one which did not do so in the first twelve hours. In the case of the staphylococcus this digestion proceeded at a fairly uniform rate; *Bacillus typhosus* and *Bacillus pyocyaneus* apparently did not attack the coagulable protein vigorously until the more easily assimilable substances had been used; *Bacillus proteus* seems to attack all the nitrogenous materials at once without discrimination. *Bacillus proteus* and *Bacillus typhosus* could both assimilate tyrosin and asparagin; *Bacillus proteus* could make use of glycocol; *Bacillus typhosus* could not.

DISCUSSION AND CONCLUSIONS

Evidently, the ability of a given cell to assimilate amino-acids does not result directly from their simplicity of structure and solubility in water; otherwise glycocol, which is the simplest and is readily soluble, would be the most easily used. We have been led to believe that the intracellular proteins synthesized by bacteria are specific, in view of various phenomena connected with immunity. It seems reasonable to suppose that this individuality may rest to some extent on the ability to absorb certain substances characteristic of those proteins. Sperry and Rettger found that pure cyrstallized proteins cannot be attacked by bacteria in the absence of decomposition products; experiments made in this department by Diehl seem to indicate that bacteria will not elaborate a ferment against a certain protein if grown on a medium containing none of the amino-acids found in that protein. The idea of individual requirements in amino-acid by various kinds of bacteria lends color and significance to these observations. We can think of the free amino-acids present in a culture containing a protein and its split products as both "building stones" in the protein molecule, and as possible "stepping stones" for the bacteria. Then the avidity with which an organism attacks a protein would be in direct proportion to the amount and variety of free amino-acids present which are represented in the structure of the protein molecule and which that particular kind of cell can assimilate. If only a few acids fulfilling both these requirements are found in the medium, the stimulus to proteolysis would not be great, at least until possibly a greater quantity and variety were set free by the first feeble attack. An organism exhibiting what might be called a catholicity of taste in amino-acids would have an increased number of approaches to the protein molecule. Further investigations will show whether or not one is justified in stating that *Bacillus proteus*, for instance, is such an organism.

In the meanwhile we are certainly justified in concluding that the nature of the particular protein decomposition products present play a very important part in metabolism, as the power to assimilate a given amino-acid is not necessarily common to all bacteria, but is due to factors which may be absent in some varieties.

STUDIES ON CHOLESTEROL

VII. METABOLIC DISTURBANCES AS AN ETIOLOGIC FACTOR IN CARCINOMA

THE INFLUENCE OF CHOLESTEROL METABOLISM AND OTHER FACTORS*

GEORGINE M. LUDEN

The problem concerns the relation of metabolic disturbances to the etiology of malignant growth. In Part I the historical evolution of the conception of malignancy as a disease of metabolic origin (that is of biochemic origin) is traced in the history of cancer research. In Part II the data and observations are discussed which led the author to share this conception of malignant disease. In Part III the findings and considerations are given which support this conception.

Specimens from operations and necropsies were studied; 3,142 permanent sections have been preserved. Chemical and other analyses were made on 2,073 individual blood samples. The samples analysed comprised the blood of human beings, of goats, gophers, dogs and rabbits, during life and taken at necropsies, besides pus, bile and food stuffs.

Blood Samples from Man under Various Conditions

	Cases	Determinations
Good health (volunteers)	57	100-150
Miscellaneous	50	50
Pernicious anemia	40	48
Hyperthyroidism (in metabolism studies)	39	39
Myxedema (in metabolism studies)	4	6 to10 each
Sarcoma	9	16
Carcinoma	223	500–600

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* Abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Pathology, 1920.

Serial Determinations on Blood

	Determinations	Time
Author	192	5 years
Patients with myxedema (4) (treated with thyroxin)	6–10 each	2 months
Patient with carcinoma of the breast	77	3 years
Patient with recurrent carcinoma of the breast, complicated by pregnancy	13	10 months
Patient with generalized lymphosarcoma (treated with radium and x-ray)	29	2 years
Patient with lupus eruthematosus degenerating into carcinoma (treated with radium)	8	7 months
Five persons without definite disease	10–24 each	6 months to 3 years

Methods Employed in the Study

Various methods of staining frozen sections, paraffin, and celloidin sections	
Bloor I and Bloor II determinations for blood cholesterol	6000 to 7000
Lewis-Benedict test for blood sugar (since June, 1919)	102
Hydrogen peroxid test for blood catalase (special technic)	116
Blood counts (total leukocytes, erythrocytes)	1118
Dare determinations of hemoglobin	1118
Differential blood counts (Wright, Pappenhein, Giemsa and other stains)	1118

Special consideration is given to (1) factors that influence the blood cholesterol, such as diet, radium, thyroxin, ulceration, and hemorrhage, (2) the effect of cholesterol on bacterial growth in vitro and in the blood, (3) the relation of the combustion products of fuel to the incidence of cancer, and (4) the interrelation of blood constituents and extraneous factors.

1. The influence of the diet on the blood cholesterol values was clearly demonstrated by the writer's dietary experiments on the writer's blood. A diet which increases the blood cholesterol (eggs, meat) coincidently weakens the "lymphoid defence." A diet composed chiefly of fruit, vegetables, cereals and milk reduces the blood cholesterol and coincidently increases the lymphoid defence, if the carbohydrate tolerance is not over-taxed. In persons predisposed to carcinoma an increase of the blood cholesterol with weakening of the lymphoid defence by prolonged use of a diet adapted thereto may further the development of carcinoma. Dietary measures calculated to reduce the blood cholesterol and to increase the lymphoid defence are of value in the treatment of carcinoma, especially as a post-operative measure.

Radium treatment reduces the Bloor I and increases the Bloor II blood cholesterol values. The Bloor I values represent the "pure" cholesterol in the blood, which is comparable to unconsumed fuel. The Bloor II values contain the "changed" cholesterol in the blood, which is comparable to consumed fuel or "ashes" in a general sense. Unconsumed fuel represents the latent possibility of conflagration: "pure" cholesterol an opportunity for undue cell proliferation as cholesterol stimulates cell division by some as yet unexplained mechanism. Changed cholesterol, like consumed fuel, does not seem to be associated with an inherent element of danger. Radium, therefore, lessens the opportunity for cell proliferation by activating cholesterol metabolism and by changing the chemical composition of the blood. It cannot be stated definitely as yet whether the activation of cholesterol metabolism is the result of the photo-active properties of radium (cholesterol is disintegrated by photo-active rays) of the stimulation of the endocrine glands by radium. It is probable, however, that the increased activity of the glands of internal secretion, resulting in the improvement of cholesterol metabolism, plays an important part in radium therapy. The high Bloor I cholesterol values found before radium treatment in many types of non-ulcerating cancers cannot be the result of increased cell destruction, as cell destruction is promoted by radium, whereas the Bloor I values are reduced.

Thyroxin, the thyroid hormone, affects the blood cholesterol in a manner somewhat similar to that of radium: it reduces the Bloor I values, but does not increase the Bloor II values to the same extent. In four cases of myxedema treated with thyroxin the blood cholesterol values and the basal metabolic rate were found to be inversely proportional: an increase of the metabolic rate was invariably accompanied by a drop of the Bloor I values, and reduction of the metabolic rate by a rise of the Bloor I cholesterol. Experimental ingestion of thyroxin by the writer gave divergent results. The experiment was repeated three times at intervals of a few months; 5 mg. thyroxin were taken each time at a single dose. Twice severe headache, tachycardia, tremor, increased perspiration and diarrhea were produced; these symptoms were accompanied by a marked drop of the blood cholesterol. The third time the ingestion of thyroxin was followed by a marked rise of the Bloor I values and only extreme lassitude and drowsiness was experienced for a few days. A similar condition of lassitude, without any symptoms of stimulation, occurred in another experimentor who took 5 mg. thyroxin at the same time; no cholesterol determinations were made in this instance, because the blood cholesterol level had not been determined before the experiment. The results obtained may be tentatively explained as follows: increased metabolic activity, produced by thyroxin, entails an increased amount of work for other endocrine glands, notably for the adrenals. Bodily or mental exertion are known to produce what has been called "adrenal fatigue." Both the other experimentor and the writer had been working particularly hard for several weeks preceding the ingestion of thyroxin; "adrenal fatigue" may therefore account for the lack of response to stimulation by the thyroid hormone. In two cases of carcinoma the administration of small doses of thyroxin, from $\frac{1}{4}$ to $\frac{1}{2}$ mg. on alternate days for one week followed by a week's interval, were found to lower the blood cholesterol and to have a distinctly beneficial effect on the general condition; one patient suffered from recurrent carcinoma of the breast involving the sternum during pregnancy: she lived much longer than her condition seemed to warrant and gave birth to a child, which has developed normally; the other patient suffered from a rapidly growing type of mammary cancer with glandular involvement and a recurrence within one year after operation was expected, but she is still free from recurrence nearly four years after operation.

Ulceration and hemorrhages reduce the Bloor I and increase the Bloor II cholesterol values. This had been observed in isolated instances and was checked systematically by the study of ninety-nine cases of uterine cancer, all of which showed ulceration and hemorrhage. As the elimination of tumor grafts in resistant animals is accompanied, as a rule, when the graft is not absorbed, by ulceration and hemorrhage, these symptoms may represent an attempt at healing on the part of nature. Ulcerative processes are known to be accompanied by febrile reactions; febrile reactions are accompanied by an increase of metabolic activities; they are known to exert a curative effect on malignant growth in many instances. The fact that radium treatment reduces both ulceration and hemorrhage may indicate that the stimulation of the endocrine glands by radium mobilizes more powerful means of defence in the body, which render the initial reaction, namely ulceration and hemorrhage, unnecessary; a similar phenomenon is observed in immunization, in which the initial febrile reaction subsides, when anti-bodies have been produced or injected.

2. The effect of cholesterol on bacterial growth is considered in connection with the work of Manfredi, who studied the influence of

cholesterol in bacterial cultures, and with the writer's observations on the changes in the blood cholesterol of five persons (serial determinations) during the epidemics of influenza in 1918, 1919 and 1920. Cholesterol inhibits the growth of pathogenic bacteria both *in vitro* and *in vivo*, although it promotes the multiplication of body cells by some unexplained mechanism. High Bloor I cholesterol values were found to accompany the onset of influenza, suggesting a defensive reaction. Two of the five persons, on whose blood weekly observations had been made during periods ranging from three to five years failed to contract the influenza; their blood cholesterol (Bloor 1) was relatively high at the time of the epidemics. The writer, whose Bloor I values were high in the beginning of 1919 did not develop the disease, although a pure culture of Pfeiffer bacilli was isolated at that time from her nasopharynx. The injection of a prophylactic serum against influenza made in 1918 produced a marked rise in the blood cholesterol values; a slightly different type of serum made in 1919 and 1920 did not produce this result to the same extent. These observations indicate that there is a relation between the blood cholesterol values and immunity. Disturbances of the cholesterol metabolism, such as have been observed in carcinoma, may account for the exacerbation of malignant conditions following influenza, the increased blood cholesterol which was intended to combat bacterial invasion being utilized for the undue multiplication of cells. The relation between the blood cholesterol and immunity deserves further consideration because of its bearing on numerous problems in medicine, among others the inexplicable occurrence of postoperative suppuration in certain cases. The writer began to study the latter problem by animal experiments, but was prevented from concluding the investigation by circumstances beyond her control (carbon monoxid poisoning).*

3. The relation between the combustion products of fuel and the incidence of cancer is considered in connection with the work of C.E. Green, C. H. Ross and R. H. Green, and with the writer's observations on the increase of combustion products in Rochester, Minnesota, and the cancer incidence among the citizens of Rochester betwen 1914 and 1918. C. E. Green found that in England, Scotland, France and the Orkney Islands the incidence of cancer is proportionate to the

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* Two of the five persons healed by first intension after a major operation; one of these two was the patient, who is free from recurrence after four years, and who failed to contract influenza, the other had influenza in 1919, but the blood of both had shown a high average at the time of operation.

amount of smoke and soot which accumulates in a given locality as the result of topographic conditions and the type of fuel that is used; he believes that it is the sulfur content of combustion products which furthers malignant cytoplasia. C. H. Ross investigated the causes of pitch cancer among briquette makers for the British Government. He came to the conclusion that the chemical composition of the "soft" grades of coal is responsible for the occurrence of pitch cancer among the workers who use this type of coal in the manufacture of briquettes and that the absence of pitch cancer in localities, where "hard" coal is used for the same purpose must be attributed to the different chemical composition of the coal. R.H. Green studied the sulfur metabolism in patients suffering from carcinoma; he found that the metabolism of sulfur is markedly impaired in this disease. The writer's observations concerning the relation of cancer incidence in Rochester to the increase of combustion products between 1914 and 1918 appear to corroborate the findings of C. E. Green. But the writer concludes that the carbon monoxid content of combustion products may play an even more important part than the sulfur content, because of the extreme toxicity of this gas, which is contained in all combustion products, and because of its demonstrably deleterious effect on the endocrine glands, notably on the adrenals. Further investigations concerning the incidence of cancer in Rochester, Minnesota, from 1908 to 1921 are in progress; they are intended to verify the afore mentioned observations and will be incorporated in this study. The great increase of combustion products from fuel and gasoline during the last twenty years and the injurious effect of these products on public health and especially on the glands of internal secretion may explain the increase of cancer to which attention has been called by many recognized authorities.

4. The interrelation between blood constituents and extraneous factors is considered in the last (twelfth) chapter of the study. The following findings may be mentioned: (a) There is an inversely proportional relation between the Bloor I cholesterol values and the total leukocyte counts; this was observed in serial tests on five persons during periods ranging from three to five years. The disintegration of leukocytes in the blood stream or elsewhere cannot account for the fact that high blood cholesterol values accompany low leukocyte counts and *vice versa*, because a marked leukocytosis (up to 21,000 leukocytes were found repeatedly in the writer's blood) is not followed during succeeding

tests by a marked rise of the blood cholesterol. Cholesterol determinations were always made simultaneously. No explanation can as yet be offered for this observation. (b) The variations in the blood cholesterol and in the blood sugar appear to run a parallel course. (c) There is a marked reduction of the blood sugar after exposure to carbon monoxid; this observation, made on four persons at different times, points, in connection with accompanying clinical symptoms, to a reduction of the functional efficiency of the adrenal glands by the toxic properties of carbon monoxid.

CONCLUSIONS

The conclusions reached in the study were:

1. The functional activity of the glands of internal secretion is a primary factor in the regulation of the chemical composition of the blood.

2. The chemical composition of the blood must affect the growth, the differentiation and the rate of proliferation of the body cells, because the life of the cell depends on its blood supply. Chemical factors must therefore play an important part in the malignant proliferation of cells.

3. There is ample evidence that the individual chemistry of the host determines the rate of growth of the tumor. This has been demonstrated experimentally by the fate of tumor grafts in animals and clinically by the occurrence and recurrence of tumors in so-called predisposed persons.

4. Recognition of the foregoing indisputable facts leads, logically, to the conclusion that the chemical conditions, which make an animal or a human body well-suited for the development of tumors, should receive the first and foremost consideration in all investigations intended to solve the problems of malignant growth.

5. It will be granted that the chemical conditions in the body are primarily the result of metabolic processes, and that normal metabolic processes furnishing normal chemical conditions are not likely to produce malignant cell proliferation, representing an impairment of health.

6. It does not seem warranted to assume that there is only one cause of cancer; because many and divers factors, such as the hereditary transmission of inadequate organs, ill-balanced diets, bacterial infections and the effect of injurious chemical agents, are each and all capable of producing an impairment of the functional efficiency of the

endocrine glands leading to abnormal metabolic and chemical conditions in the body.

7. Admission of the foregoing premise, however, transfers the problems of malignant growth from the domain of histology to the realm of biologic chemistry; it reduces the importance of the structural imperfections of the cell unit and emphasizes the importance of the chemical conditions under which the cell unit is forced to exist; it compels us to look on malignant neoplasia as the result of abnormal chemical conditions, furnished by abnormal metabolic processes; it discredits the conception of cancer as a local disease; it vindicates the conception of malignant growth as a disease of metabolic origin.

8. Determinations of the blood cholesterol are of special value in the study of malignant growth, because cholesterol promotes the multiplication of cells. The mechanism by which cholesterol furthers cell proliferation has not yet been fully explained, but the following facts are evidence, that cholesterol plays an important part in cell formation and cell division. (a) During the process of hatching the cholesterol content of the egg-yolk is utilized for the formation of the cells which constitute the body of the chick embryo. (b) During gestation, both in human beings and in animals, the increase of the cholesterol content in the mother's blood is most marked at the time when the growth of the fetus is the most rapid; under normal conditions the mother's blood cholesterol returns to its normal level after the offspring has been born. (c) Addition of cholesterol to the culture medium accelerates cell division in paramecium from three to five-fold. (d) Intravenous injections of cholesterol in tumor-bearing rats have been found to double the rate of growth of the tumor grafts. (e) Disturbances of the cholesterol metabolism occur in malignant conditions, notably in cancer; they are characterized by an increase of the blood cholesterol and a reduction of cholesterol disintegration. (f) Cholesterol metabolism is stimulated and improved by radium therapy of which the beneficial effects in malignancy need no comment. (g) Cholesterol metabolism is intimately associated with the total basal metabolic rate as shown by the relation between basal metabolism and the blood cholesterol values in myxedema and hyperthyroidism. (h) Diseases, in which high blood cholesterol values are common and persistent, are clinically known to be frequently associated with cancer. But the test for cholesterol in the blood is not a diagnostic test for malignancy; it is merely a clinical test capable of

giving valuable information about cholesterol metabolism, that is, the way in which the body is handling its cholesterol.

9. Cellular pathology, which looked on cell morphology as the key to the cancer problem, has neither revealed the cause, nor found the cure for cancer, but the patient labors of the pathologist have paved the way for the future work of the chemist.

10. Chemical analyses are the logical mode of attack in the study of any disease caused by chemical disturbances. The progress of modern chemistry warrants that a more general admission of the biochemical etiology of malignancy and researches along chemical lines will solve the problems of malignant growth, because scientific achievements have always been controlled by the technical facilities which investigators had at their command. Biologic chemistry will find the cure for cancer.

NOTE.—Forty-four illustrations, photographs, photomicrographs of specimens, and charts of the chemical analyses accompany the thesis.

X

GENERAL

LIBERATION OF ANTIBODIES ON INJECTION OF FOREIGN PROTEINS*

SIEGFRIED F. HERRMANN

Many reports have been published concerning the treatment of acute and chronic infections by the intravenous injection of foreign proteins. This treatment has been applied to typhoid fever, arthritis, and certain skin diseases. It apparently developed as an outgrowth of the injection of vaccines. Vaccine therapy, once the great hope of modern therapeutics, failed to produce the promised results, and, with the exception of prophylactic vaccination against typhoid, variola, rabies, and perhaps in acne and allied pyogenic skin diseases, was being abandoned more and more. Now there is an apparant revival of allied therapeutic methods in the form of foreign protein injections.

The beginning of foreign protein therapy dates back to the work of Fraenkel in 1893, who treated fifty-seven cases of typhoid fever with subcutaneous injections of typhoid vaccine. He reported that most of the cases were favorably modified, and that a few terminated by rapid lysis. This use of typhoid vaccine during the active, acute stage of the disease was a new departure, which demanded further investigation.

Rumpf, using a vaccine of Bacillus pyocyaneus, repeated the work in another group of cases, and observed equally favorable results.

Ichikawa, using intravenous injections of sensitized vaccine, and Kraus and Mazza, using polyvalent vaccine, were able to produce favorable modifications in 60 per cent of their cases. They also observed equally good results in paratyphoid and found that colon vaccine could be substituted for the typhoid vaccine.

More recent work on typhoid has been reported by Lüdke with albumoses; Saxl, using a solution of caffein and camphor; Kibler and McBride, using typhoid vaccine, and so forth.

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The bibliography is herewith omitted.

Foreign protein has been used also in the treatment of arthritis. Notable is the report of Miller and Lusk. Miller later summarizes his results and gives an extensive bibliography of work done by other clinicians. The results as reported appear promising, especially in acute arthritis.

Other favorable results have been reported in skin diseases, puerperal sepsis, conjunctivitis, iritis, trachoma, typhus, tuberculosis, and so forth. Among the variety of proteins employed are: colon vaccine, chicken serum, whole blood, proteose, albumose, horse serum, and autolyzed vaccine.

Closely related to the response to foreign protein is the old and familiar observation that a specific disease may sometimes improve with the advent of some intercurrent infection. For example, the symptoms of acute gonorrhea have been observed to subside with the incidence of typhoid fever. Attention has also been called to the increased resistance of the body to various common infections, following any vaccine injection.

It is evident that foreign protein therapy is empirical and nonspecific. Almost any foreign protein seems to be effective, and may be employed more or less successfully, under suitable conditions, in a variety of diseases. The question arises as to what factor is responsible for the apparent benefits observed. If this manner of treatment is to be placed on a scientific basis this factor must be determined. Clinical investigations have thrown no light on this question. The type of reaction is apparently the same in all cases.

As described by Kibler and McBride the reaction of a typhoid patient to the intravenous injection of typhoid vaccine is as follows:

Temperature.—Within a few minutes to one hour after the injection a chill occurs, lasting from twenty to thirty minutes. This is followed by a rapid rise of temperature which later falls abruptly, and then tends to remain remittent in favorable cases.

Leukocytes.—Usually there is an early leukopenia within four hours, due mainly to a disappearance of polymorphonuclears. Within about twelve hours this is followed by a moderate polymorphonuclear leukocytosis.

Blood pressure is usually decreased by from 10 to 15 mm. after the chill.

Coagulation time.—Only slight and insignificant changes have been observed.

Antibodies.—No essential difference from the specific response to the injection of typhoid antigen in a normal individual was observed in these typhoid patients It is to be noted, however, that conditions here differ somewhat from those in which an heterologous protein is injected.

The reaction in arthritis cases agrees essentially in the first four particulars with the reaction in typhoid fever. The antibody response will be considered later. Most clinicians seem agreed in regarding the severe chill as the most important factor in this reaction. It is evident that the chill alone cannot be responsible for the marked relief from pain and for the remission in the course of an acute arthritis. It is possible, however, that the resulting hyperpyrexia may have an effect in favoring immune reactions and antibody production.

Rolly and Meltzer, in a study on the effect of high temperatures, injected a series of rabbits with small doses of typhoid bacilli or cholera vibrios. Some of these rabbits were kept in an oven so that their body temperature remained between 40° C. and 42° C. The controls were kept at ordinary room temperature. They observed a higher average production of agglutinins and lysins in the high temperature rabbits than in the controls. They also showed that phagocytosis by human leukocytes in vitro occurs at its optimum between 37° C. and 40° C.

More recently, Winslow, Miller and Noble investigated the effect of moderately high temperatures on the production of lysins against sheep blood corpuscles. They kept their rabbits in an oven at a moderately high temperature, 29° C. to 32° C. Injections of sheep cells were given and the hemolytic titer estimated each week. They found that the rate of lysin production in the heated rabbits was slower than that in the controls.

These experiments may indicate that a moderately high temperature lowers the general vital resistance to a beginning infection. Once an infection is established, however, according to Rolly and Meltzer's results, hyperpyrexia may bring about a greater production of antibodies.

If a specific leukocytosis could be observed, one might think that this would be a factor in overcoming the infection, but the degree of leukocytosis seems only to parallel the severity in each case. Gay and Claypole believed that a specific hyperleukocytosis occurred in typhoid immune rabbits, following injections of typhoid bacilli, but

McWilliams later showed that both normal and immune rabbits respond to about the same degree. The leukocytosis therefore cannot be regarded as specific.

The slight variations in blood pressure and coagulation time are evidently insignificant.

We pass now to a consideration of the antibody response. Very little work on this aspect of the question has been done, yet it seems as if the explanation of a therapeutic response, in the case of any infection, to the injection of a substance not specifically bactericidal to the infecting organism, should logically be sought in the liberation of specific antibodies against that organism. Ordinarily when the body overcomes a streptococcic infection, for example, we believe this is accomplished by the production of antibodies against the streptococcus. Why, then, should we not suspect that the therapeutic effect of foreign protein injections in infections, obviously not due to the foreign protein *per se*, has as its basis the liberation of specific antibodies against the causative organism? In the case of arthritis we believe that the symptoms persist because the antibodies which should normally be produced are for some reason not liberated.

In the light of Ehrlich's receptor theory, we recognize three distinct phases in the production of antibodies: (1) the sensitization of the tissue cells; (2) the overproduction of sessile receptors; (3) the liberation of these receptors from the cells. A perfect antigen is one which causes all of these phases to be completed. It seems a plausible hypothesis that in those cases of arthritis add so forth, which show a rapid therapeutic response to injections of foreign protein, the etiologic organism is acting only as an imperfect antigen. It sensitizes the cells and causes sessile receptor production, but does not give the necessary stimulus to cause these receptors to be thrown off. The foreign protein then supplies this stimulus, the system is flooded with specific antibodies, and a remission of the infection results. Although a variety of proteins may serve to complete this second phase, the reaction is still absolutely specific, since there must be a specific stimulation of cells, and a final liberation of specific antibodies.

In this connection I would recall the experiments of Bruck. According to Ehrlich's theory a molecule of tetanus toxin is composed of a haptophore group, which unites with the cell receptor, and a toxophore group, which is responsible for the poisoning of the cell. This toxophore group can be destroyed by various methods such as heat, light, and long preservation. The toxin has then become a toxoid. The haptophore group can still unite with a sessile cell receptor, or with a specific antibody, but because of the absence of the toxophore group the molecule has become innocuous. Bruck injected rabbits with small repeated doses of such a toxoid. The rabbits were found to produce very little, or no free antitoxin, the amount being dependent on the amount of effective toxophore groups which still remained in the toxoid. He further showed that rabbits injected with tetanus toxoid, during the first few succeeding hours possessed a greater tolerance for tetanus toxin, but that later they showed an actual hypersensitiveness, being killed by only a fractional portion of the ordinary lethal dose of toxin.

These results Bruck interpreted as follows: The haptophore group of the toxoid at first is anchored to the specific cell receptor. The toxin molecule introduced soon afterward, therefore, cannot reach the cell, since all the receptors are blocked. Later, however, an overproduction of sessile receptors occurs, and a hypersensitiveness to toxin results, since the avenues of approach to the cell are increased many times. The toxoid has acted as an inferior antigen. It has brought about the first and second steps of antibody production, namely, (1) sensitization of cell receptors, and (2) the overproduction of similar sessile receptors, but it has lacked the necessary stimulus to cause the discharge of these receptors. Had the rabbits been immunized with small doses of unchanged toxin this third stage would have been completed. Bruck therefore sees in the toxophore group the necessary stimulus for the setting free of the receptors. Might not a foreign protein, in an analogous way, supply such a stimulus? It was with this hypothesis in view that I undertook an investigation of the effect of foreign protein on antibody production. The experiments have been conducted entirely with rabbits, because all the factors can thus be much more accurately controlled than in a purely clinical investigation.

Several other investigations have been reported which touch on the immune reactions in foreign protein therapy.

Jobling and Petersen report a "mobilization of ferments," notably protease and lipase, following foreign protein injections. Later they point out an "increase in antiferment," dependent on "highly dispersed, unsaturated lipoids," and conclude that "the main therapeutic factor is probably an increased dispersion of colloids."

Culver investigated the opsonin and lysin content in the serum of patients with gonorrheal arthritis, after intravenous injections of gonococcic vaccine and proteose. He reports a rise in titer of these antibodies.

Bull reports a rise in the antibodies of typhoid immune rabbits after the injection of typhoid bacilli; but his results could not be confirmed by Teague and McWilliams, who suggest a new theory to explain the therapeutic effect on cases of typhoid, of intravenous injections of typhoid vaccine. On the supposition that blood serum is more bactericidal than lymph, they base the theory that the vaccine causes a greater flow of bactericidal serum into the lymphoid organs, and thus overcomes the local infection. It does not appear that this theory has been substantiated.

On the basis of the hypothesis that the foreign protein reaction serves as a stimulus to set free specific antibodies, I first investigated opsonins for the streptococcus. This organism is notably a poor antigen, in that it is difficult to obtain a high antibody titer against it. An animal sensitized with this organism should therefore be a favorable subject for the liberation of antibodies by foreign protein.

Series 1.—Two rabbits were injected intravenously at three-day intervals with 1 c.c. of a fresh suspension of killed *Streptococcus viridans*. The organism was grown on blood agar slants, and a twenty-four-hour growth washed off with 10 c.c. salt solution. This emulsion was heated at 60°C. for one hour to kill the bacteria, and 1 c.c. of this vaccine used as a dose. A fresh vaccine was made each time. The fourth injection consisted of 0.5 c.c. of living streptococci. Five days later the opsonic index was determined, and 2 c.c. of human ascitic fluid injected intravenously.

The method of determining the opsonic index was that of Wright, using the experimenter's own leukocytes and serum as a standard.

Both rabbits were found to have a very low opsonic index five days after the fourth injection of streptococci; 2 c.c. of human ascitic fluid were then injected, and a marked rapid rise of opsonins occurred, the total increase being 700 per cent in forty-eight hours. Apparently the foreign protein acted as an effective stimulus to liberate sessile receptors.

After eighteen days the opsonic content was again found to be at a low level. Two further injections of streptococci were then given. This time an interesting variation in response occurred. The opsonic index of Rabbit 17 rose, while that of Rabbit 311 continued to fall. In the former the streptococci evidently acted as a perfect antigen, causing all three stages of antibody production, while in the latter the final liberation of antibodies did not take place. This supposition was confirmed by the effect of an injection of ascitic fluid. In Rabbit 17 there resulted no further increase in opsonins. The stimulus of the antigen had been sufficient to liberate all antibodies. In Rabbit 311 a rapid liberation of opsonins followed the foreign protein injection. In this case we picture the tissue cells as loaded with an overproduction

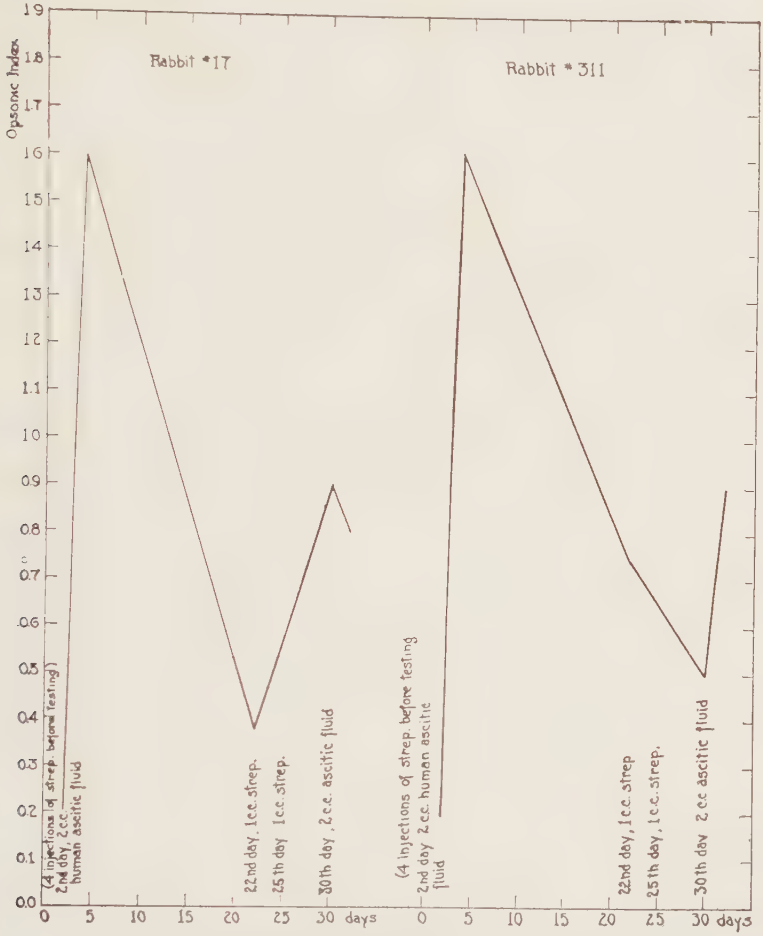

Fig. 199 (Series 1).—Opsonins for streptococcus.

of specific sessile receptors. The foreign protein reaction then acted as an effective stimulus to cause the cells to throw off these receptors.

Series 2.—In this series two rabbits were injected with fresh suspensions of meningococci, and human serum was used as foreign protein. Rabbit 395 received two injections of serum with a resulting rise after each injection. Apparently the cells were not completely desensitized by the first serum injection. Rabbit 268 received no second injection and showed a gradual decrease in opsonins.

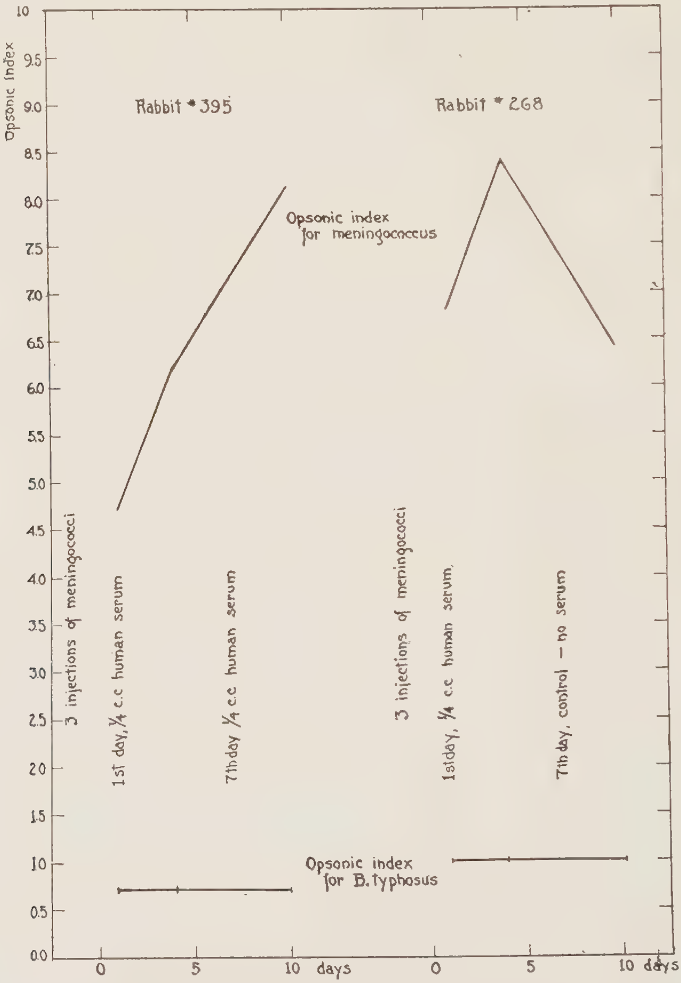

Fig. 200 (Series 2).—Opsonins for meningococcus.

In order to demonstrate whether these antibodies were specific for meningococci, and also as a control of the technic, the serums were also tested each time for opsonins against *Bacillus typhosus*. The typhoid opsonic index remained low and unchanged throughout.

Series 3.—Two rabbits were given four intravenous injections of *Streptococcus viridans* at three-day intervals, as in Series 1. Six days after the fourth injection the opsonic index was determined. Rabbit 31 then received 1 c.c. of human serum intravenously, while Rabbit 32 was used as a control and received no serum. The former showed a rise of 38 per cent on the third day following, while the op-

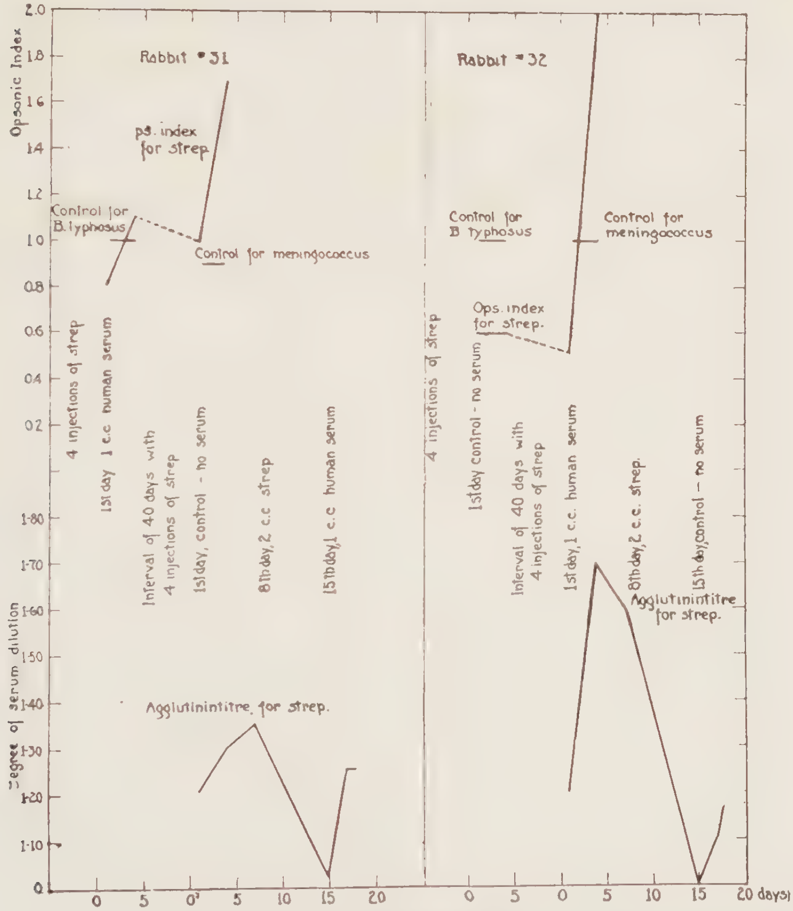

FIG. 201 (Series 3).—Opsonins and agglutinins for streptococcus.

sonic index of the latter remained stationary. The control test for Bacillus typhosus remained unchanged in both cases.

During the next forty days four injections of a dextrose broth culture of streptococcus were given. Six days after the last injection the opsonic index was again determined. It was found lowered in both rabbits. Rabbit 32 then received 1 c.c. of human serum. There followed a rise of nearly 300 per cent. Rabbit 31 showed a spontaneous rise, but to a much less degree. A check opsonic determination for meningococci showed no variation.

It was now thought that if an increase in opsonins occurred, following foreign protein injection, it should also be possible to demonstrate a simultaneous rise in the agglutinin titer for streptococci.

The agglutinin titer was determined by the microscopic method as follows: The rabbits were bled from the ear veins, the blood allowed to clot, and the serum separated by means of rapid centrifuging. Varying dilutions of the serum were then made in 0.9 per cent salt solution. Hanging drop preparations were made by placing on a coverslip, with a small platinum loop, one drop each of diluted serum and of a fifteen-hour dextrose-broth culture of streptococcus. The coverslips were then inverted on vaselined hollow ground slides, and left at room temperature. Readings were then taken under the microscope at the end of three hours. Positive agglutination could be observed in the lower dilution, consisting of definite clumping of the streptococcal chains. The highest degree of dilution in which a positive test occurred was recorded as the agglutinin titer.

The first tests were made simultaneously with the last opsonic determinations. In response to the first serum injection Rabbit 32 showed a rise in agglutinin titer of 250 per cent. Rabbit 31, which served as a control at this time, also showed a slight rise (50 per cent) and continued to rise gradually. The agglutinin titer of Rabbit 32 began to fall after the third day. All the sessile receptors apparently had been freed by the foreign protein injection, while in Rabbit 31, without the stimulus of foreign protein, they were liberated to a less degree and more slowly.

In order to resensitize the tissue cells 2 c.c. of broth culture were now injected. Seven days later the aglutinin titer had fallen very low in both rabbits. This time Rabbit 31 received 1 c.c. of human serum, while Rabbit 32 served as control. A rapid rise of agglutinin titer occurred in the former which then remained stationary. In the control rabbit a more gradual rise occurred. Thus the specific response to the foreign protein injection was again observed.

Series 4.—It now became necessary to investigate whether or not foreign protein injections would serve to bring about a mobilization of antibodies against an organism which was known to be a good antigen, that is, one which when injected into an animal, would readily cause the production of a high titer of free antibodies. The typhoid bacillus is known to be such a perfect antigen, when injected into rabbits. Indeed, it is not unusual to obtain an agglutinin titer against typhoid as high as 1:500,000 dilution.

Two rabbits were injected repeatedly with emulsions of typhoid bacilli until they showed an agglutinin titer of 1:50 on testing by the macroscopic method; 1 c.c. of guinea-pig serum was then injected and the agglutinin titer again determined in forty-eight and seventy-two hours. No rise in titer was apparent.

Further injections of typhoid bacilli were then given until the agglutinin titer reached 1:100. Then 0.5 c.c. of human serum was injected. Again no increase in agglutinins could be observed during the next seventy-two hours. A second injection of human serum did not change the titer.

In order to check these negative results two more rabbits were immunized with typhoid bacilli. After two injections of bacilli the agglutinin titer was found to be zero by the microscopic hanging drop method, as described under Series 3; 0.5 c.c. of human serum was then injected, and the antibody titer again determined on the third day following. Again no agglutinins were found. Evidently the rabbits had not yet been sufficiently sensitized against the bacilli.

Immunization with typhoid bacilli was then continued until the microscopic method revealed an agglutinin titer of 1:3,000; 2 c.c.of human ascitic fluid were then injected intravenously. No rise in agglutinin content resulted.

The serum of these rabbits was also tested for complement fixing bodies, with the idea in mind that the foreign protein reaction might possibly bring about a liberation of such antibodies, although it apparently had no effect on the agglutinin content.

As an antigen in the complement fixation test an old suspension of typhoid bacilli in salt solution, to which 0.3 per cent tricresol had been added, was used. The test was carried out with the usual technic, using this typhoid antigen, washed sheep blood cells, fresh guinea-pig complement, and rabbit amboceptor. The serum of the typhoid immune rabbits was inactivated by heating at 56 C. for one-half hour, then diluted, and the fixing power of a given quantity tested. It was found that the ability of the inactivated serum to fix complement was not changed in the slightest degree by foreign protein injections.

We must conclude that foreign protein injections have no effect on the antibody production in typhoid immune rabbits. The typhoid bacillus is apparently a perfect antigen in rabbits, and no foreign protein is needed to stimulate the liberation of antibodies against it.

How, then, can we reconcile this with the apparent therapeutic benefits observed in some human patients? May it not be possible that some patients do not react completely to the antigenic stimulation of the typhoid bacillus? In such cases the foreign protein might well serve as a stimulus causing the sensitized cells to throw off their sessile receptors. This sudden flooding of the system with antibodies might then be responsible for the remission in the disease. This hypothesis seems to be supported by the succeeding series.

Series 5.—Thus far I have recorded observations on opsonins and agglutinins. It seemed desirable also to investigate the response of a third type of antibodies, lysins, to foreign protein injections. Since it is difficult to make accurate determinations of the lysin content of a serum for a specific bacterial cell, we decided to use as our antigen washed sheep corpuscles. A hemolytic titer can be very accurately obtained, while a bacteriolytic titer, obtained by the method of extinction and plating, is modified by too many possible errors of technic.

It is well known that rabbits will readily produce lysins against sheep corpuscles. Common use is made of this fact in producing amboceptor for the hemolytic system of the Wassermann reaction. We may say, therefore, that sheep cells act as a good antigen when injected into rabbits. This would allow us to predict, on the basis of the preceding series, that foreign protein injection into rabbits sensitized against sheep cells would have little effect on the liberation of specific lysins. It has, however, been frequently observed in this laboratory that a great variation exists in the readiness with which different rabbits will produce amboceptor when injected with sheep cells. Rubinstein recently studied the hemolytic titer of rabbits after three injections of sheep red cells. The titer was determined before each injection, and seven days after the third. He found that of eleven rabbits only eight showed a definite marked rise in lysins after each injection. In one of the remaining three the titer remained the same, and in the other two there was even a decrease in lysin content after successive injections. In such rabbits as the latter three the sheep cells evidently acted only as an inferior antigen, and in such cases we would expect, on the basis of our previous work, to be able to liberate antibodies by means of foreign protein injections.

The hemolytic system in these experiments consisted of 0.10 c.c. fresh guinea-pig complement (diluted 1:10), 0.5 c.c. of a 2 per cent suspension of fresh washed sheep corpuscles, 1.5 c.c. of 0.9 per cent salt solution, and graduated amounts of inactivated rabbit serum. The least amount of serum that would cause complete hemolysis after incubation at 37° C. for one hour was recorded as the lysin titer.

Twenty rabbits were used in this series. The rabbits were injected intravenously with two initial doses of sheep corpuscles in salt solution. As a rule the lysin content was then measured from ten to twelve days after the last injection, it having been determined that the lysin titer normally reaches its height by the end of this period. After foreign protein injections, either human serum or typhoid vaccine, the lysin content was again determined, usually in seventy-two hours, in order to give ample time for any resulting change in titer to take place.

In Rabbit 386 sheep cells evidently acted as an inferior antigen, the lysin content eleven days after the second injection being very low and remaining so; 0.25 c.c. of human serum injected on the seventeenth day after the last injection did not influence the lysin content. Believing that this was due to the fact that the tissue cells were no longer properly sensitized, another injection of sheep cells was given. Eleven days after this the titer was still at the same low level. An injection of foreign protein (typhoid vaccine) was then given, and an immediate marked liberation of lysins occurred. These antibodies disappeared rapidly. A second injection of typhoid vaccine in seven days had no effect on raising the lysin titer, but the curve continued to fall rapidly. A third injection of red cells was then given and this time acted as a perfect antigen. The lysin content rose to its height in ten days and remained high for several days. After it began to decrease another injection of red cells was given, but this time an injection of ascitic fluid was given only four days later, in order to determine whether an early stimulation by foreign protein would serve to liberate antibodies. A very pronounced mobilization of lysins followed.

This alternating introduction of red cells and foreign protein was continued. Every time the mere injection of antigen (red cells) failed to produce lysins in the rabbit serum a mobilization of these antibodies could be effected by foreign protein. When, on the other hand, there was a normal response to the antigen, the foreign protein was followed by no further liberation of lysins. After the last two injections of red cells apparently all the receptors were not spontaneously liberated because there was a slight response to foreign protein ten days later.

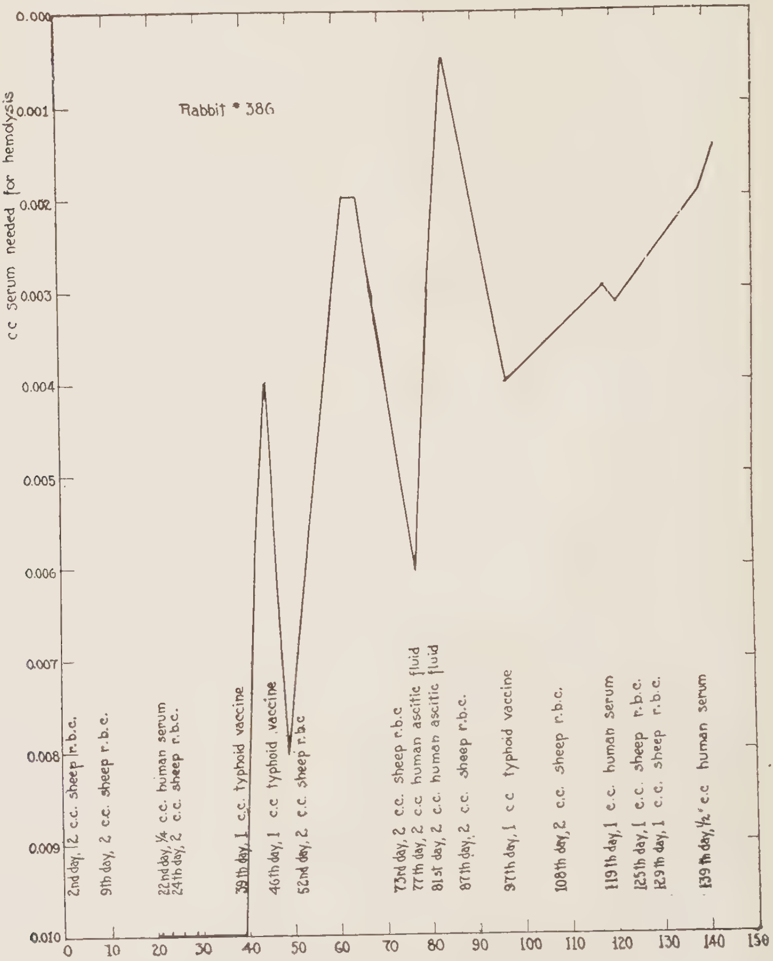

FIG. 202 (Series 5).—Lysins for sheep cells.

Rabbits 387 and 362 were of the same type, as they failed to respond to injections of red cells by a proper production of antibodies, but when then injected with foreign protein a marked liberation of lysins occurred.

Rabbits 30 and 39 responded very well to the antigenic stimulation of sheep cells; Rabbit 39 was used as a control, while Rabbit 30 received human serum on the eleventh day following the last injection of antigen. No marked difference was noted in the reactions of the two rabbits. This was observed also in a number of other cases. When the titer is already high, foreign protein will not bring about a further rise in antibody content.

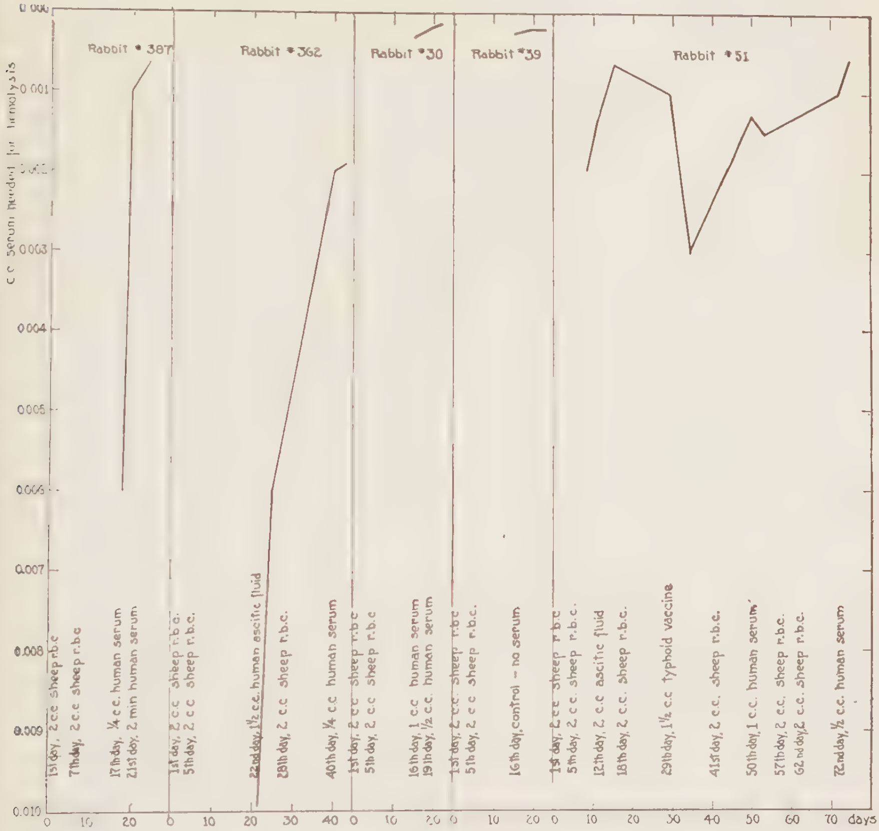

FIG. 203 (Series 5).—Lysins for sheep cells.

Rabbit 51 represents a negative result which cannot be readily explained. The typhoid vaccine injected on the twenty-ninth day should have been followed by a rise in antibodies, according to our other observations, since the red cells eleven days earlier had not produced a liberation of lysins. In other respects, however, this curve is in accord with the general results.

SUMMARY

In rabbits sensitized with streptococci a definite liberation of specific opsonins and agglutinins follows the injection of foreign protein.

A similar rise in specific opsonins also occurs in rabbits sensitized with meningococci.

Foreign protein injections have no effect on antibodies in typhoid immune rabbits.

In suitable rabbits, which do not readily produce lysins against sheep corpuscles, the injection of foreign protein within ten days after the injection of antigen is followed by a marked liberation of specific lysins.

A variety of foreign proteins can be used. Human serum, typhoid vaccine, human ascitic fluid, and guinea-pig serum proved equally efficacious.

CONCLUSION

The intravenous injection of foreign protein serves as a stimulus for the liberation of specific antibodies in animals in which the previously injected antigen is unable to cause such a liberation. This insufficiency may lie either in the antigen or in the rabbit.

PERMEABILITY OF BACTERIA*

ROBERT G. GREEN

On the basis of the popular conception that changes in the electric conductivity of a system comprised of cells surrounded by a solution of an electrolyte are an index of the permeability of the cells (and the plasma membrane of these cells in particular) to the ions of the electrolyte present, an investigation was conducted to determine changes in the permeability of bacterial cells when heated to a degree sufficient to produce sterile suspensions.

The measurement of these changes in conductivity was made by means of a Wheatstone's bridge. The source of current was a panel type Vreeland oscillator and a current of 450 cycles was employed. The bridge wire was of the rotary type and very delicate readings were obtained by the use of a variable inductance in series with the conductivity cell which contained the bacterial suspension. The temperature was regulated to $1/25$ degree Centigrade by an electrically controlled thermostat. The conductivity cells used in these experiments had the form of an inverted T and had a capacity of about 2 mils.

The method of investigation was to study not only the changes in resistance of the system comprised of the bacterial cells and the surrounding solution of electrolyte, but also the changes in each member of the system. This was accomplished by centrifuging the bacterial cells and measuring the resistance of the electrolyte solution, following which the bacterial cells were again thrown into an even suspension and the resistance of the system measured. The concentration of the electrolyte surrounding the cells, the time of heating the suspension, and the degree of heat (58°C. to 96°C.) applied were varied in different experiments.

The experimental results are summarized as follows:

1. A solution of an electrolyte containing bacterial cells offers greater resistance than the solution alone.

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* Abstract of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Arts, 1919.

2. On heating, the resistance of a suspension of bacterial cells decreases, and above the thermal death point of the bacteria, the decrease is independent of the temperature.

3. On heating, the resistance of the solution surrounding the bacterial cells decreases an amount which is about 75 per cent as great as the decrease observed in the suspension of which the solution was a part.

4. Centrifuging and remixing a freshly heated suspension results in a decrease in the total resistance of the suspension below that found immediately after heating but before centrifuging. This drop in resistance does not occur if a heated suspension is treated in a similar manner a second time and does not occur with suspensions of live bacteria.

5. The effect of heating a constant volume of bacteria in each of a series of solutions of varying concentration of electrolyte gives results exactly analogous to those obtained by adding a constant amount of additional electrolyte to each of the series.

These experimental results tend to show that:

1. The change in electric conductivity of a system of cells and a surrounding solution of an electrolyte is due in greater part to changes in conductivity of the surrounding liquid and not to changes in the permeability of the cells themselves to the ions moving by virtue of the existing electric current.

2. When bacterial cells die electrolytes are given off into the surrounding medium and the magnitude of their effect depends on the concentration of the solution in which they are given off.

3. The electrolytes are not all given off by the cell into the solution immediately on heating. On centrifuging the maximum amount of electrolytes passes from the cell into the solution.

4. If bacterial cells are heated in a solution of such concentration that no change occurs in the surrounding solution, such solution is probably isotonic with the interior of the bacterial cell.

5. Dead bacterial cells when added to a solution of an electrolyte cause an increase in resistance which is about 75 per cent of the increase which occurs when the cells are alive and added to the same solution. Bacterial cells, therefore, after death are not almost completely permeable in a manner which can be demonstrated by electric conductivity as has been claimed for bacterial cells, sea urchins eggs, plant cells, and cells of other types.

A STUDY OF THE THRUSH PARASITE*

BERTHA CECELIA FINEMAN

The organism of thrush has not been studied thoroughly. There is confusion in the literature concerning its morphology and botanic position, and with regard to the unity or plurality of species.

In the body the organism of thrush appears in yeast-like or filamentous form. In culture mediums usually only the yeast-like form appears, but at times mycelium is also observed. Various theories have been advanced to explain this dimorphism. Linossier and Roux have claimed that the complexity of form increases in proportion to the complexity of the carbohydrates in the medium. Stumpf believed that the filamentous and yeast-like forms were two different species of fungi. Hinkle observed that the amount of free oxygen influenced the morphology, an abundance of oxygen giving rise to the yeast-like form, a decrease producing mycelium.

The organism has been placed in various genera of fungi by various authors. A critical examination, however, indicates that there is no real basis for confusion except between the genera *Endomyces* and *Oidium*. The distinction between these two depends on the presence or absence of ascospores. Their presence has been claimed by Vuillemin and by Fisher and Brebeck. In the work here reported an attempt has been made to verify the presence of ascospores and to determine the conditions which may give rise to mycelial or unicellular forms in culture mediums, and also by means of sugar fermentation reaction and agglutination tests to determine whether there is but one species or a number.

The results of these studies are summarized as follows:

1. Seventeen strains of the thrush parasite proved identical and constant in their morphologic and cultural characters. They all corresponded to the nonliquefying type of Fisher and Brebeck.

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* Abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Arts, 1920.

This thesis is published in full in the Journal of Infectious Diseases, 1921, xxviii, 185–200.

2. Carbohydrate mediums were fermented uniformly and constantly by all strains. They are of value in the identification of the species.

3. Agglutinins are not produced by the thrush parasite in sufficient quantity to be of diagnostic or differential value.

4. The thrush parasite produces chlamydospores but not ascospores. It is correctly placed in the genus *Oidium.*

5. The organism tends to assume mycelial form in liquid mediums, in mediums containing complex carbohydrates, in mediums of low oxygen tension, and in mediums of low surface tension; while the unicellular or yeast-like form occurs in solid mediums, in the presence of simple carbohydrates, of an abundance of oxygen, or in mediums of higher surface tension. These factors may be interrelated while other factors as yet unknown may affect the morphology. It is suggested that the pleomorphism of this organism is an attempt at adaptation, the mycelial form developing in relatively unfavorable conditions.

STUDIES ON THE GEOTROPISM OF THE MARINE SNAIL, LITTORINA LITTOREA*

SAKYO KANDA

The reactions to light and gravity of the common marine snail, *Littorina littorea*, were studied in apparatus permitting of movement on a glass surface placed at various measured angles with the vertical. Experiments were made in water and air, and in light and darkness.

From the experimental results it is concluded that the phenomenon of the negative geotropism of *Littorina littorea* cannot be explained adequately by the mechanical theory, the pressure theory, or the resistance theory, and that the surface-film theory also is not correct, but that it is explainable by a physiologic theory, that is, the statocyst or statolith theory, particularly since these snails have statoliths. The latter theory is not accepted on direct evidence, however, but largely by the method of exclusion.

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THE DEVELOPMENT OF THE SUPRAPERICARDIAL (POSTBRANCHIAL, ULTIMOBRANCHIAL) BODY IN SQUALUS ACANTHIAS*

WALTER E. CAMP

From a review of the literature it is obvious that most investigators consider the ultimobranchial body homologous with the suprapericardial body of selachians. In this group little work has been done on the suprapericardial body since the original communication in 1885 of its discoverer, Van Bemmelen. Owing to the absence of any complete description of the gland in a single form of the lower vertebrates, and because of the singular position it occupies among glands when classified according to form, it was thought that a detailed study of its development and structure in a single form (Acanthias) would be desirable.

The present paper is based upon a study of a series of sectioned embryos of *Squalus acanthias* from 19 mm. to 95 mm. in length and of sections and dissections of the glands of a number of specimens of 'pups' (late fetuses), newborns, and adults. The results of the study may be summarized as follows:

1. The suprapericardial body of the gland in Acanthias appears in embryos of about 20 mm. in length. It arises as an outpouching of the epithelium of the ventral pharyngeal wall, medial and slightly caudal to the sixth gill-pouch. In its position and mode of development the gland corresponds to the ventral extremity of a rudimentary seventh pouch.

2. The epithelial outpouching forming the anlage of the gland rapidly develops into a solid connecting-stalk and a blind, expanded ventral portion. The dorsal part of the connecting-stalk remains as a diverticulum from the pharyngeal epithelium. The remaining part of the connecting-stalk and the expanded ventral portion of the gland become converted into large, distended vesicles, most of which intercommunicate, but some of which are completely isolated. A part of

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the gland in the adult may secondarily become connected with the pharynx by a true duct. In its development and structure, therefore, the suprapericardial body represents a type of gland intermediate in structure between the ordinary branching gland and the closed follicular or typical ductless gland.

3. The early development of the gland is always limited to the left side. The right gland is inconstant in its development and does not appear until about the 33 mm. stage. When the right gland is present it has the form of a single cyst or solid cord of cells which degenerates completely in the course of development.

4. The vesicles of the adult gland are derived from branching tubules which develop from the expanded ventral portion of the gland and the connecting stalk. The process of formation of the new tubules can, for convenience of description, be divided into three stages: (a) A small, but definite, localized proliferation of cells at the site of the future tubule. (b) An extension of the lumen of the parent tubule into the new cell mass, the cells of which rotate so as to become placed radially with respect to the new lumen. The newly-formed outpouching may remain connected and grow *en masse* with the parent tubule, forming a branching tubule. (c) The newly-formed outpouching may become constricted off by ingrowth of the epithelial walls from one or both sides. The nuclei of the cells of the ingrowth become placed tangentially with respect to the circumference of the lumen, but when the tubule is completely separated they rotate through an arc of 90° to assume a position radial to the new lumen.

5. Throughout the later development of the gland and in the adult, the tubules and vesicles are closely surrounded by a rich plexus of thin-walled veins which drain laterally into the inferior jugular trunk. Accompanying the veins and imbedded in some cases directly in their wall is a network of vessels which have been interpreted as lymphatics. The lymphatics and veins communicate freely and are analogous to the venæ lymphaticæ and vasa lymphatica of the thyreoid of selachians, as described by Ferguson.

6. The vesicles are lined by a single layer of narrow columnar cells which are actively secreting mucus. The nuclei are elongated oval or rod-shaped and located in the basal portion of the cells. In the adult the secretion of a part of the gland is conveyed to the pharynx by a small duct. The secretion of the greater part of the gland is, however, stored in the vesicles and may be taken up by the vasa lymphatica.

GROWTH OF THE BODY AND OF THE VARIOUS ORGANS OF YOUNG ALBINO RATS AFTER INANITION FOR VARIOUS PERIODS*

CHESTER A. STEWART

In the study of the growth of the body and of the various organs of young albino rats after inanition for various periods, eight litters, comprising forty-five rats were used, of which nine were controls. Of the test rats, three were repeatedly starved and refed for short intervals. The others were refed after various periods of maintenance (from the age of three weeks to the ages of four, six, ten or twelve weeks). At the end of the experiments the rats were killed and necropsied.

The experiments showed that in young rats the marked tendency of the body as a whole to recover its weight after a period of maintenance is likewise characteristic of the various organs and parts. The abnormal proportions produced by underfeeding rapidly disappear on generous refeeding, so that practically the normal relations are restored in most cases within four weeks. This readjustment evidently involves a modification of the growth curves of many of the various organs and parts of the body during the early refeeding periods. Thus, those organs and parts which lose weight during maintenance grow more rapidly than the body as a whole, whereas those which gain weight during the maintenance period show a tendency to lag behind until the normal balance is restored.

The more important results of the investigation are summarized as follows:

The average daily gain in weight of the young rats refed after being held at constant body weight for short repeated periods was somewhat higher than that of the controls. This enabled the test rats to make up lost time and to overtake the controls, but not to exceed them in body weight.

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For data on the effects of longer and more severe inanition see Jackson, C. M. and, Stewart, C. A.: The effects of inanition in the young upon the ultimate size of the body and of the various organs in the albino rat. Jour. Exper. Zool., 1920, xxx, 97–128.

The average daily loss in weight did not increase in the rats on successive periods of severe fasting, involving a loss of 25 per cent of the initial weight.

The increment of body weight on refeeding the test rats after each severe fast amounted to only about 16 per cent of the ingested food (exclusive of water).

The amount of food required daily for maintenance decreased during the first fifty days of the experiment, but after that time apparently no further diminution occurred.

The growth in body weight of the rats refed after maintenance for various periods averaged for some time considerably higher than the normal for the (younger) controls of corresponding initial weight. Thus the stunted rats were able to overtake the full-fed controls in body weight before the end of the normal growth period. No effect of the stunting on the ultimate body weight was noted in these experiments.

As to the body proportions, the relative weights of the head, trunk and extremities remain practically normal during the various periods of refeeding.

Of the systems, the musculature and "remainder" continue practically normal for corresponding body weight during the various periods of refeeding. The integument rapidly increases, and the skeleton decreases, in relative weight, so that both reach approximately the normal proportions within the first two weeks of refeeding after maintenance from three to twelve weeks of age.

The viscera which are known to lose weight during maintenance, the thymus, spleen, thyroid, lungs and ovaries, likewise apparently regain their normal relative weights within two weeks after refeeding. The thymus, and possibly the lungs, spleen, and ovaries, are apparently even above normal (over-compensatory growth) at four weeks of refeeding, but all are found practically normal in the rats refed to the adult stage.

The viscera whose weight remains nearly constant during maintenance, the brain, heart, kidneys, liver, and epididymides,—in general present approximately normal proportions during the process of refeeding, although the heart appears slightly above normal and the epididymides somewhat below.

The viscera whose weight increases during maintenance, the eyeballs, spinal cord, alimentary canal, hypophysis, testes and suprarenals have in general decreased in (relative) weight so as to approach the normal within the first four weeks of refeeding. The testes and the suprarenals may even become subnormal in weight during the first four weeks of refeeding, but all are practically normal in the rats refed to the adult condition.

The pineal body is approximately normal in weight in the test rats refed four weeks, and in the adult test animals. There was no evidence of a sexual difference in the weight of the pineal body in rats of corresponding body weight.

CHANGES IN THE RELATIVE WEIGHTS OF THE VARIOUS PARTS, SYSTEMS, AND ORGANS OF YOUNG ALBINO RATS UNDERFED FOR VARIOUS PERIODS*

CHESTER A. STEWART

In the study of the changes in the relative weights of the various parts, systems, and organs of young albino rats underfed for various periods, eighty-nine albino rats were used, including thirty-four control rats and fifty-five test rats. Of the controls seven were dissected at an average net body-weight of 10 gm., four at 3 gm., fourteen at 15 gm., one at 27 gm., one at 40 gm., four at 50 gm., and three at 70 gm. The majority of the test rats were starved for intermittent periods by removing them from the mother, twenty-four to forty-eight hours after birth. Seventeen rats were dissected at the age of three weeks, nine at the age of six weeks, and thirteen at the age of ten weeks. The average net body-weights at these ages were approximately 10 gm., 13 gm., and 15 gm., respectively. In addition, sixteen rats, starting at three weeks of age, were underfed for much longer periods (139 to 412 days). The general plan was to kill the test rats, whenever possible, at the same body-weight as the corresponding controls.

The more important results of the investigation may be summarized briefly as follows:

Newborn albino rats are able to withstand separation from the mother for nearly one-half of the total time or the usual nursing period of three weeks, resulting in great retardation of the normal growth of the entire body.

During the underfeeding, the tail in the test rats elongates more rapidly than the body, thus producing relatively long-tailed individuals.

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The eyelids in the test rats open at a body weight lower than that of the controls, but the time of opening is somewhat delayed.

The weights of the extremities are but slightly, if at all, changed in the test rats during short and during very long fasting periods. The head apparently increases slightly in weight, especially during the very long fasts, the increase being compensated by a slight decrease in the weight of the trunk. The results of the fast on the various systems are as follows:

The skeleton shows a considerable increase in weight in the test rats. The growth apparently proceeds along the lines of normal development, as indicated by a decrease in water-content, the appearance of third molar teeth, and by formation and fusion of various epiphyses.

The musculature in the majority of test rats increases slightly in weight.

The visceral group, as a whole, shows a considerable increase in weight in the test rats underfed from birth to three, six and ten weeks. During the longer fasts there is apparently a less definite change, with a tendency to decrease in the majority of cases.

The integument remains practically normal in weight in the rats underfed from birth to three weeks, but shows a marked loss in weight later. Although the integument as a whole loses weight in rats underfed to ten weeks of age, the external ear continues to grow considerably, and tends to assume the normal adult appearance. The continued growth of the ear is probably associated with the persistent tendency to growth of its skeletal (cartilaginous) portion.

The "remainder" appears to decrease in the rats underfed to three weeks of age, which is partly compensated for by skeletal increase. During the longer fasts there is a slight increase in the weight of the "remainder" in the majority of cases.

In general, therefore, in young rats subjected to prolonged inanition, there appears to be a progressive tendency in the skeleton and, to a slight extent, in the musculature to increase in weight, counterbalanced by a decrease in the integument and viscera. The individual organs of the visceral group vary greatly, however.

In general, it appears that in rats underfed from birth up to three, six, and ten weeks, there is a marked increase in the weight of the spinal cord, eyeballs, liver, stomach, and intestines (empty). A less marked tendency to increase occurs in the brain (especially in the earliest period), heart (progressive increase), spleen (at six and ten weeks), intestinal contents (at six and ten weeks), suprarenals (progressive increase), kidneys, testes, epididymides (at three and six weeks, loss later), ovaries and hypophysis.

There is no marked change in the weights of the thyroid and pineal glands. A marked loss in weight occurs in the lungs and especially in the thymus. In the earliest period only (up to three weeks) there is a loss in the weight of the spleen and intestinal contents.

In the rats underfed for very long periods (starting at three weeks of age), the well-marked increase is maintained in the weight of the spinal cord, of the eyeballs, and usually of the suprarenals. The brain also shows a slight increase. In the case of the lungs, however, the apparent increase is of doubtful significance. There is apparently no marked change (or inconstant variability) in the weights of the intestinal contents, kidneys, ovaries, testes (?), and pineal body. The thyroid, thymus, heart, liver (variable), spleen (variable), alimentary canal (empty), epididymides and hypophysis (in males) usually suffer a loss in weight during the long underfeeding periods.

THE EFFECTS OF INANITION IN THE PREGNANT ALBINO RAT, WITH SPECIAL REFERENCE TO THE CHANGES IN THE RELATIVE WEIGHTS OF THE VARIOUS PARTS, SYSTEMS, AND ORGANS OF THE OFFSPRING*

LEE W. BARRY

That a restriction of the diet of the mother during pregnancy usually results in a decrease in the weight of the offspring has long been known. Prochownick (1899, 1901) obtained a marked reduction in the weight of the human newborn by a restriction of the mother's diet during the last weeks of pregnancy. Rudolski (1893) starved rabbits and a dog during pregnancy and noted a reduction in the size of the offspring. Paton (1903) underfed pregnant guinea-pigs and obtained a marked reduction in the weight of the young. Reeb (1905) underfed rabbits and dogs during pregnancy and obtained young greatly reduced in weight. However, none made observations on the changes in the relative weights of the various organs, systems, and parts of the newborn which might occur during inanition of the pregnant mother. The main object of this investigation, therefore, is to show the effect of inanition in the pregnant albino rat on the changes in the relative weights of the various systems, organs, and parts of her newborn. Observations were made also on the possibility of blighting of the ovum, death of the fetus *in utero*, prolongation of gestation, abortions, and premature deliveries during inanition of the mother.

MATERIALS AND METHODS

For the present investigations, two series of adult female rats (*Mus norvegicus albinus*) were used for inanition during pregnancy. Those in series A are adult females from the colony at the Institute of

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Anatomy, which were kindly given over to my use by Dr. C. M. Jackson; Series B consists of adult females from several sources. A few were reared from normal litters in Series A; some were purchased from a local animal dealer, and others were obtained from the departments of physiology and psychology of the University. Unfortunately, however, the exact age of very few of the females was known.

Breeding.—Since the influence of inanition on the length of gestation was to be noted, and in order to exclude the possibility of some of the small rats being the result of premature birth, it was very important to know the approximate date of copulation.

Three methods were used:

1. Kirkham and Burr (1913) have shown that the female albino rat usually ovulates within twenty to forty-eight hours after the birth of a litter, and impregnation occurs one to four days after the casting of a litter. A few of my females became pregnant by this method, the males being left with the mother during the second night following delivery. This method was abandoned, however, since out of a very large number of females delivering only a few became pregnant.

2. The second method was to place several males alone in small wire cages and once each day the different females were placed with the males. If the female was in heat, copulation usually took place at once. The female was not removed at once, but was left with the male for a period varying from fifteen minutes to one hour. If not in heat, the female usually resented the advances of the male, in which case she was removed and replaced by another female. After successful pairing with the male, the female was weighed. Her weight, together with her number, was recorded, and she was placed in a cage with other females that had paired. It was found better to place the female in with the male, because when the process was reversed the male, suddenly finding himself thrust into a strange cage, paid very scant attention to the female, but would spend all his time attempting to escape from the cage. The majority of the females were paired by this method.

3. The third method employed consisted in placing several males in a cage with a number of females. They were left together constantly and inspected at intervals of six hours during the day and once, in the evening. When a female in the cage became in heat, the males would copulate with her with such frequency that in a short time the vagina became distended, reddened, and at times bled slightly. After a

little experience, the females that have copulated may be distinguished by the distended, reddened, and at times slightly bloody vaginal orifice.

Period and severity of starvation.—In the beginning of the investigations it was decided to starve one group of females throughout pregnancy and another group during the last half only. The results from starvation were so disappointing that this was abandoned. Of seventeen females that had been observed to copulate and were starved from this time for periods varying from sixteen to twenty-six days, only one gave birth to a litter, four died, and the others were so weakened that they were saved only with difficulty. In the second group fifty-nine females were starved severely during the last half of pregnancy (or suspected pregnancy), beginning on the eleventh day after copulation. The animals were weighed daily and their weights recorded. The amount of food (usually not more than 1 gm.) which they received daily varied with their loss in weight and general condition. The food consisted of whole-wheat bread (graham) soaked in whole milk (Table 1). Water from the city supply was allowed in the cages at all times.

Prevention of mother's eating young.—A difficulty soon experienced was the eating of the young by the starving mothers. Early in the investigation several of the mothers ate and mutilated their newborn young, rendering them worthless for dissection purposes. Various muzzles were devised but without success. The method finally adopted was to place the pregnant female in a cage with a wire bottom, the meshes of which were 1 cm. square, thus allowing the newborn rats to drop through onto a clean piece of paper beneath. Thus, not only were the newborns saved for dissection, but any abortions or premature deliveries might be noted.

Throughout the period of inanition the pregnant females were kept in a specially warmed room in order to prevent death from chilling or pneumonia.

Necropsies.—In this investigation ninety-nine rats were necropsied, sixty of which were from mothers underfed during the last half of pregnancy, twenty-nine were normal fetuses removed from the recently killed mother, and ten were normal newborns. In order to compare the effect of prenatal inanition in the newborn rat (test), it was necessary to compare this test rat with a normal (control) fetus of the same body-weight from an unstarved mother.

The mothers from which the control fetuses were obtained were chloroformed. After death the abdomen was slit open and the fetuses and placentas removed from the uterine horns. The fetus was removed from the amniotic sac and the umbilical cord severed by crushing in order to prevent bleeding, close to the belly wall. The fetus was quickly wiped dry of excess fluid, killed by chloroform, measured, weighed, and dissected. These are designated the "prenatal controls." The "test rats" are newborn rats from the underfed mothers. The "normal newborns" are newborn rats from normal litters.

The series and number of the mother, the number of the litter, and the order in the litter for each individual dissected is shown in Table 4. A or B with the number following denote the series and number of the mother in the series; the number following this denotes the number of litters the mother has borne during the experiment, while the number following the decimal point denotes the number of the individual rat in the litter. For example, B2 2.1 shows that the rat was number 1 in the second litter from the mother number 2, Series B.

It will be noted that these rats (Table 4) are arranged in five groups in accordance with their net body-weights. Group 1 contains the test rats and prenatal controls whose net body-weights range from approximately 2 gm. to 2.5 gm.; Group 2, those ranging from 2.5 gm. to 3 gm.; Group 3, those ranging from 3 gm. to 3.5 gm.; Group 4, those ranging from 3.5 gm. to 4 gm., and Group 5, those ranging from 4 gm. to 4.5 gm. This grouping was done in order to facilitate computations and to render apparent any variations according to the size of the rats. Since no sexual differences were found in the organs and parts, the sexes are combined in the groups and computations. All computations were made on the average weights of the organs and parts.[1]

All the test rats necropsied were born by the natural method, although the length of gestation was occasionally prolonged.

The necropsy technic was the same as that described by Jackson and Lowrey (1912) and Jackson (1913), with a few modifications. Their technic was as follows:

After killing with chloroform, the gross body-weight and lengths of body (nose-anus) and tail were recorded. The head was removed on a plane just anterior to the larnyx and posterior to the cranium, and weighed. The trunk was suspended, thus allowing the blood (unmeasured) to escape. The eyeballs and brain were then removed and placed in a moist chamber. The trunk was next dissected and the viscera removed and weighed individually in the following sequence: thyroid gland, thymus, heart (opened and blood clots removed), lungs, liver, spleen, stomach and intestines (including contents, mesentery and pancreas, also weighed without contents), suprarenals, kidneys, gonads, and spinal cord. The extremities were removed at the shoulder and hip joints and weighed. The skin was next removed from the trunk and extremities and weighed; the skeleton and musculature were weighed together; then the musculature was dissected off and its weight determined by subtracting the weight of the skeleton from the combined weight. As soon as possible after the birth of the inanition test-rats, and immediately after the removal of the prenatal controls from the mother, they were killed by chloroform, if not already dead. Each was then placed on its back and extended by allowing one end of a steel ruler (300 mm. by 35 mm. by 2 mm., weight 263.5 gm.) to rest on the abdomen and neck. In this way the amount of extension was found to be much more constant than by trying to hold the body extended by means of the hand. The distance from the tip of the nose to the anus (nose-anus length) and from the tip of the tail to the anus (tail-length) was carefully measured by calipers and the distance read off on a millimeter scale.

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[1] The original individual data are filed and available for reference at the Wistar Institute of Anatomy, Philadelphia.

Jackson and Lowrey weighed the stomach, intestines, and pancreas together with the mesentery. In my investigation, however, the stomach, intestines, and pancreas were weighed separately. The technic was as follows:

The rat was placed belly down and the skin, muscles, and other tissues dissected from the left lumbar region and an incision made through the peritoneum just below the costal margin. By gentle pressure on the abdomen, the stomach, spleen, and part of the pancreas were forced through the opening. The spleen was now easily separated from the stomach and pancreas and placed in a moist chamber. The stomach was freed from its attachments to the liver and pancreas, seized at its juncture with the esophagus with a small pair of forceps, firmly compressed to prevent the escape of any of the gastric contents, and severed at that point and also at the pylorus. The stomach was then weighed in a closed container, opened, its contents allowed to escape, and the interior cleaned with moist filter paper, after which it was reweighed. The intestines were removed as described by Jackson and Lowrey (1912) and weighed with and without their contents, after the pancreas had been removed. By subtracting the weight of the contents from the body-weight, the net body-weight was obtained, and this was used as a basis for computations.

It was found that the "gold dust" preparation, used by Jackson (1915) to free the skeleton of its periosteum and ligaments, acted too strongly on the delicate skeletons in my series, resulting in a loss of the cartilages. Consequently, the skeletons were cleaned as thoroughly as possible of muscles and ligaments merely by dissection. These are designated as "moist" skeletons. The moist skeletons were dried for one month (to a constant weight) in an oven at a temperature of 85°C. to 95°C. to obtain their dry weight.

GENERAL EFFECTS OF UNDERFEEDING

Blighting of ovum.—In one experiment seventeen female albino rats were underfed for varying periods of from sixteen to twenty-six days from the time of observed copulation. Only one (A 6) gave birth to a litter after twenty-four days. This mother received daily 10 gm. of food until the eleventh day after copulation, and thereafter 1 gm. daily until delivery, starvation being severe only in the last half of pregnancy. Her fetuses were necropsied and included with the data. Of the seventeen rats, four died of starvation. Necropsy revealed no pneumonia or other disease.

In another series fifty-nine females were underfed from the eleventh day after copulation to delivery, death, or the discovery of no existing pregnancy. Of this number, nineteen (32 per cent), (Table 1), gave birth to litters; twelve (20 per cent) died during pregnancy (Table 2); and twenty-seven (46 per cent) did not give birth to litters (Table 3).

Huber (1915) found in the rat on the sixth day after copulation, localized thickenings of the uterine mucosa, sufficient to cause localized swellings of the uterine tube. Stotsenburg[12] (1915) has shown that on the thirteenth day of pregnancy the average weight of the rat fetus is 0.040 gm. It is interesting to note that in my pregnant rats it was found that the swellings in the uterine horns could be palpated through the abdominal wall of the living animal between the tenth and eleventh days after copulation. None of the females (sixteen) underfed from the time of copulation, and not having litters, showed swellings in the uterine horns at any time palpable through the abdominal wall. In the twenty-seven females (Table 3) observed to copulate and underfed from the eleventh day thereafter (no litters resulting), swellings in the uterine horns were palpated in fifteen, doubtful swellings in three, and no swelling in nine. Of the twenty-seven animals, five died during the starvation period; four of these were necropsied, one (A 63) showed definite swellings in the uterine horns (two in the right, and three in the left, about 8 mm. in diameter), the other three showed no macroscopic evidence of pregnancy.

Microscopic examination of sections of the uterine swellings in A 63 revealed a mass of degenerating tissue with no evidence of a fetus. One female, B 64, was refed ten days after being underfed twelve days and was killed. At necropsy four swellings in the left and five in the right uterine horn were found, averaging about 1 cm. in diameter. Microscopic examination of these showed a mass of degenerating tissue with no evidences of fetal tissue. Apparently these were cases of blighted ova or early embryos. What was the fate of the swelling palpated in the other rats starved? Were they absorbed? This question needs further investigation.

It is significant to note that of the seventeen females starved from the time of copulation, only one became visibly pregnant and no swellings were ever palpated in the remaining sixteen. Does starvation early in pregnancy inhibit implantation by lessening the amount of pabulum or embryotroph necessary to the nourishment of the ovum, or by uterine circulatory changes or a condition of acidosis? Or does it cause a blighting of the ovum after implantation? This also needs further investigation.

Length of gestation.—According to Stotsenburg[41] (1914), the length of gestation in the non-lactating albino rat varies from twenty-one days and fifteen hours to twenty-two days and sixteen hours. The length of gestation in my starved rats varied from twenty-one days to twenty-six days; eight of the total of twenty-two were above the twenty-three-day limit, six with a gestation-period of twenty-four days, one of twenty-nine days, one of twenty-six days. Thus, severe inanition during the last half of pregnancy usually lengthens the duration of gestation comparatively little. This is rather surprising, in view of the fact that King (1913) found the gestation period markedly lengthened in pregnant nursing rats. King says:

> "The period of gestation is always prolonged when a female is suckling six or more young. In these cases the number of young in the second litter seems to have less influence on the length of the gestation period than has the number of young suckled, but if both litters are very large, the gestation period may be extended to thirty-four days."

Daniel (1910) in investigations on the mouse, formulated the following law (quoted by King, 1913, as "Daniel's law"): "The period of gestation, in lactating mothers, varies directly with the number of young suckled."

Both Daniel and King seem to have overlooked the work on the prolongation of gestation in different species of rats by Lataste (1891), in which he states:

> "On voit que, d'une facon générale et sauf perturbations accidentelles, le retard de la gestation, dans une même espèce, est proportionnel au nombre des petits allaités, un nouveau jour de retard correspondant à un nourisson de plus."

He proved that the retardation of gestation was due to a delay of the implantation of the ovum during the first six to ten days of pregnancy, due probably to a lack of proper nourishment for the ovum as it enters the uterine cavity. He found that traumatizing the mother early in pregnancy markedly prolonged gestation, while at later periods there was no effect. This is in harmony with my observation that there is very little prolongation of gestation in starvation during the latter half of pregnancy.

Abortion and premature delivery.—Although my females were kept in cages with meshed-wire bottoms, so that the products of conception might fall through, no abortions or premature deliveries were observed. Rudolski (1893), in inanition experiments on rabbits and a dog, stated that premature deliveries seldom occurred, and that abortions were never observed. Prochownick (1901) cites forty-eight cases in which women were placed on a restricted diet during the last half of pregnancy, with no abortions or premature deliveries resulting. He also reviewed the earlier literature on the subject. Paton (1903) observed no abortions or premature deliveries in guinea-pigs starved during pregnancy. Reeb (1905) observed premature deliveries in two rabbits starved from the beginning of pregnancy, but none in rabbits or dogs starved during the last half of pregnancy.

Although no abortions or premature deliveries were observed, it is interesting to note that five of the twelve females that died during pregnancy (Table 2) began to bleed from the vagina from one to three days before the end of the normal gestation period. In one of these, B 64, the fetuses had evidently been dead for some time, since on section and microscopic examination of the swellings in the uterine horns, a degenerating mass of material was found, in which no fetal structures were distinguishable. Rat B 58 (Table 2), killed after refeeding ten days, showed a similar condition in the uterine horns; but the death of the fetuses evidently occurred earlier, as the swellings of the uterine horns were smaller (5 mm. to 8 mm. in diameter, compared to 9 mm. to 15 mm. in diameter in B 64).

Macroscopic examination of the placentæ of the rats dying after hemorrhage revealed no separation of the placentæ and no evidence of beginning labor. Are these cases to be regarded as beginning abortions in which the fetuses have died *in utero* and therefore analogous to missed abortions occurring in the human being? This subject requires further investigation, checked by careful microscopic examination to determine whether this bleeding is due to beginning abortion or is the result of degenerative changes in the placenta itself, or perhaps to changes in the maternal blood.

Sterility.—From the total number of seventy-six female rats starved during pregnancy (or suspected pregnancy), only four became pregnant a second time (B 2, B 29, B 43, and B 44, Tables 1, 2, and 3). Of the seventy-six starved, twenty-one died, a mortality of 27 per cent. Although the remaining fifty-five were placed with the males frequently, only four (7 per cent), became pregnant after starvation. Thus it appears that inanition during pregnancy produces a condition of sterility in the majority of the females. Whether this sterility is absolute or only temporary can not be stated, because a sufficient period has not elapsed since the starvation of many of the females.

Jackson and Stewart (1919) likewise found that starvation in young female rats produced sterility in a large number.

Stillbirths and viability of the newborn.—From the data in Table 1, it is seen that from a total of 129 newborn young rats from mothers starved during pregnancy, forty-one were found dead after delivery. Whether these were dead *in utero*, died during delivery, or afterwards, it is impossible to state. At birth, the newborn dropped through the wire bottom of the cage, and as many were born inclosed within the amniotic sac, death may have resulted from suffocation. The living seemed to be quite vigorous. As they were necropsied as soon as possible after birth, no statements can be made concerning their viability and after-life. King (1916), however, has made a study of the growth of albino rats undersized at birth (one a female weighing but 2.6 gm.). She states:

> "A very small weight at birth indicates that a rat has a handicap in its organization, that environment, however favorable, can not overcome. Such animals, although they appear vigorous and healthy during their growth period and after reaching the adult state, are unquestionably subnormal in regard to the size of the body and the central nervous system."

Size of litters.—The average number of young per litter observed in the rats starved during pregnancy was 5.9. King (1915) found an average of 7.0 per litter in 1,089 litters. Apparently starvation during the last half of pregnancy has at least no marked effect on the number of young per litter.

Weight of fetus. Rudolski (1893) starved rabbits and a dog during pregnancy and found that on one-half to one-third of their normal diet the mothers gave birth to healthy, normal offspring and that at times these litters even exceeded in weight the litters from mothers on a normal diet. However, on greater reduction (one-fifth to one-thirtieth) of their normal diet, the mothers gave birth to young many of which were born dead or died soon after birth. The body dimensions were reduced in size. The offspring were toothless and gelatinous in structure, showing a poor development of the subcutaneous tissues and a marked reduction in the amount of fat.

Prochownick (1901), in a report of forty-eight cases in which women with contracted pelves were placed on a restricted diet during the last months of pregnancy, found the weight of the newborn to be markedly reduced. The average birth-weight was 2,960 gm. and 2,735 gm., respectively, in twenty-four males and twenty-four females. Thus, the males were 11 per cent to 14 per cent and the females 14 per cent to 15 per cent below the average weight for that part of Europe (Hamburg). The length, head circumference, and ossification of the cranial bones were not affected. There was, however, a reduction in the amount of subcutaneous fat.

Paton (1903), in a series of female guinea-pigs kept on a low diet during pregnancy, found the average weight of the litters to be 28 per cent below that in mothers kept on a normal diet.

Reeb (1905) obtained a marked reduction in the size of the young in rabbits and a dog placed on a reduced diet during the last half of pregnancy. Although the pregnant rabbits suffered an average loss of but 7.1 per cent in body-weight during inanition, the individual newborn showed a reduction of 20 per cent to 60 per cent in weight as compared with young from the same mothers on a full diet. The dog lost 8.1 per cent during starvation in pregnancy and the individual young showed a loss of 29 per cent as compared with controls from the same dog on a normal diet.

All the experiments were carried out by a quantitative reduction in diet. Evvard (1912), however, has shown that undersized young with lessened vigor and vitality result when young pregnant sows (gilts) are fed on corn alone, in large quantities, but unsupplemented by a diet rich in ash and protein. He attributes this reduction in size and vigor of the offspring chiefly to a lack of calcium salts in a diet of corn alone. Later, Evvard, Dox, and Guernsey (1914) found that normal litters resulted if the corn diet was supplemented by calcium chloride (or calcium carbonate) and blood protein.

Hart, McCollum, Steenbock, and Humphrey (1919) fed a diet of corn, grain, and wheat straw to pregnant heifers. The resulting offspring were weak and often dead-born. However, when a suitable salt mixture was added to the diet, normal calves resulted. Osborne and Mendel (1914) have shown that the corn kernel is deficient in certain salts and amino acids which are necessary to normal growth in the rat.

From my data on the weights of individual rats from mothers starved during the last half of pregnancy, the average gross weight of the newborn is approximately 3 gm. The average gross weight of the normal newborn rat in the same dolony has beed found to be approximately 5 gm. (Stewart, 1919), the average in my ten normal newborn being 4.92 gm. Consequently, underfeeding during the last half of pregnancy apparently causes a reduction of about 40 per cent in the average birth-weight of the newborn albino rat. The gross body-weight of the individual test rats ranged from 2.1 gm. to 4.4. gm. The average percentage loss of weight of the mother during starvation (Table 1) was 28 per cent, the loss ranging from 11 per cent to 39 per cent. There is no constant relation between the loss in body-weight of the mother and the size of the newborn or the number in the litter. However, it should be noted that in general the percentage loss of weight was greatest in the heaviest rats which frequently bore the heaviest fetuses. Also, as might be expected, the weight of the newborn tends to be inversely proportional to the loss in the weight of the mother. Thus, the heaviest newborns (4.3 gm.) were from a mother losing only 11 per cent in weight.

Just what effect this loss or retardation in birth-weight has on the relative weights of the various parts, systems, and organs of the newborn rat, or other animals, has not hitherto been ascertained, so far as appears from the available literature. These effects of prenatal starvation, and a comparison of the results obtained in postnatal starvation, will now be considered for the various organs and parts. In each case the data for the normal newborn will be given first; then the prenatal norm, and finally the condition in the corresponding groups of test rats will be compared. This will enable us to see whether, in these stunted test rats with retarded body-weight, the various parts retain their normal proportions, as found in the normal, younger, fetuses of the same body-weight; or, if not, the character and extent of the disproportions which have arisen. Finally, a comparison will be made with the known effects of postnatal inanition.

RELATIVE WEIGHTS AND LENGTHS OF BODY PARTS

Ratio of body-weight to body-length.—In the ten normal newborn rats dissected, the average body-length was 51 mm., net body-weight 4.92 gm.; Stewart (1919), using litters from the same colony, found the average body-length to be 50.3 mm., net body-weight 5.03 gm.

The ratio of the body-weight in grams to the body-length in millimeters in my newborns was 0.096. In Stewart's series (1919) the ratio is 0.099. The Wistar norm ratio (Donaldson, 1915) is 0.10 for a 51 mm. rat. In my prenatal fetal controls (Table 5), the ratio of the body-weight to the body-length is 0.061 in Group 1, and increases through all the groups until in Group 5 it is 0.092. The ratio for the test rats in Group 1 is 0.061 and increases through all the groups at nearly the same rate as the prenatal controls to 0.089 in Group 5.

By comparing the prenatal and newborn norms, it is found that the smaller the fetus *in utero*, the smaller is the figure representing the body-weight to body-length ratio; in other words, the younger the fetus (from 2 gm. to 4.1 gm.), the less the weight per millimeter of body-length. The test rats follow this same law, the ratio being very similar to that in the corresponding normal controls of the same weight or length. Therefore, it may be stated that the growth ratio, or the relation between fetal body-weight and body-length, is not disturbed by starving the mother during pregnancy.

Ratio of tail-length to body-length.—The ratio $\frac{\text{tail-length}}{\text{nose anus length}}$ is called the "tail ratio." In my normal newborns the tail ratio $\frac{\text{tail-length, 16.4 mm.}}{\text{body-length, 51 mm.}}$ is 0.311 (sexes combined). Stewart (1918*a*), in litters from the same colony, found a tail ratio of 0.318 (sexes combined). Jackson (1915*a*), using litters from both Minnesota and Missouri, found a tail ratio of 0.36 in the newborn (sexes combined). The tail ratio for the prenatal controls in Group 1 is 0.339 (all females); for the test rats, 0.324; for the controls in Group 2, 0.288, for the test rats, 0.310; for the controls in Group 3, 0.313, for the test rats 0.327; for the controls in Group 4, 0.300, for the test rats, 0.326; for the controls in Group 5, 0.296, and for the test rats, 0.323. The tail ratio for the prenatal norm averaged for all five groups is 0.307; for the test rats, 0.322. From these data it is apparent that the ratio of the tail-length to the body-length during the later prenatal growth of the rat (from 2 gm. to 4.1 gm.) is about the same as that found at birth; also that inanition in the mother during pregnancy has very slight influence on the tail ratio of the offspring.

If the absolute data are directly compared, the tail-length in the test rats in all the groups (Table 5) is slightly above that of the prenatal norms of the same average body-weight, being 2.8 per cent above in Group 1 and 13.1 per cent on Group 5, showing an average gain of 6 per cent above the norm in all the groups combined. This gain in tail-length, therefore, appears to be less marked in the smaller rats, becoming greater as the size of the body approaches that normal at birth. It agrees with the observations of Jackson[19] (1915) and Stewart (1918), that postnatal starvation in growing rats tends to produce relatively long-tailed individuals.

Head.—Jackson and Lowrey (1912) give the weight of the head in the newborn albino rat as 1.147 gm., or 21.65 per cent of the body-weight, 5.3 gm. (sexes combined). In my normal newborn series the weight of the head is 1.041 gm., or 21.2 per cent of the body-weight, 4.92 gm.

In my prenatal controls, the average weight of the head forms 24.2 per cent, 23.0 per cent, 22.7 per cent, 21.0 per cent, and 20.5 per cent of the body-weight in Groups 1, 2, 3, 4, and 5, respectively (computed from Table 5). Thus, in the prenatal controls the head has a higher relative weight in the smaller than in the larger rats, which fact agrees very well with the law formulated by Jackson (1909): "A relatively large embryonic head is characteristic of vertebrates in general." The head in the smaller prenatal controls also has a higher relative percentage weight than in the normal newborns, the difference decreasing with the increase in the weight of the prenatal controls.

In my test rats the average weight of the head forms 24.0 per cent, 24.1 per cent, 23.5 per cent, 22.3 per cent, and 22.0 per cent of the body-weight from Group 1 to Group 5, respectively (computed from Table 5). Therefore, the relative weight of the head is slightly higher in the test rat than in the prenatal controls, except in Group 1.

The absolute weight of the head in the test rats exceeds that of the corresponding prenatal controls by 2.8 per cent, 6.0 per cent, 3.8 per cent, 6.5 per cent, and 7.6 per cent in Groups 1, 2, 3, 4 and 5, respectively, averaging 5.3 per cent above in the test rats. Thus in prenatal inanition the head shows a slight increase in weight, which is due partly to the increase in weight of the brain, eyeballs, and the integument covering the head.

In postnatal inanition in young rats, a stronger tendency for the head to increase in weight, even when the body-weight has been held constant, has been noted (Table 6). Stewart (1918*a*) found the head to increase 45 per cent in weight (as compared with controls of the same body-weight) in rats held at a constant body-weight from birth to sixteen days. In a series of rats stunted by underfeeding from birth to three weeks (body-weight 10 gm.) the average increase in the weight of the head was 16 per cent, as compared with controls of the same body-weight. In rats underfed from the age of three weeks to ten weeks, there was an apparent increase in head-weight of 2.1 per cent as compared with controls of the same body-weight (Jackson,[19] 1915). This slight gain in weight is attributed to the slight gain in skeletal weight, which in the head probably overbalances the loss in weight of the integument.

In both acute and chronic inanition in adult rats, the head increases markedly in relative weight and loses slightly in absolute weight (Jackson,[18] 1915).

From the foregoing it appears that the head manifests its strongest relative growth tendency in rats underfed from birth to sixteen days. That this growth tendency, though apparently less intense, is present before birth is evidenced by the increase of the head-weight of the test rats as compared with prenatal controls of the same body-weight.

Extremities and trunk.—In my normal newborn series, the fore limbs form 7.0 per cent and the hind limbs 7.6 per cent of the body-weight, 4.92 gm. This is a lower relative weight than given by Jackson and Lowrey (1912) for the relative weight of the extremities in the newborn rat of 5.3 gm., their figures being 7.39 per cent and 9.45 per cent for the fore and hind limbs, respectively. This difference is probably due to a variation in technic. Although the fore and hind limbs were always severed from the body at the shoulder and hip joints, respectively, it was extremely difficult to leave the same amount of skin and muscle attached to the limb in each case.

In my prenatal controls, the fore limbs form 5.3 per cent, 6.8 per cent, 7.4 per cent, 6.7 per cent, and 7.1 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the fore limbs in the smaller prenatal control fetuses is less than in the normal newborn, but this difference, in relative weight, decreases with the increase in the size of the fetus.

In the test rats, the fore limbs form 6.8 per cent, 6.8 per cent, 7.2 per cent, 7.3 per cent and 7.1 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus, with the exception of Group 1, in which the relative weight of the fore limbs in the tests quite markedly exceeds that of the prenatal controls, there is very little difference in the relative weights in the fore limbs of the test rats and prenatal controls, in both of which the fore limbs form a relatively smaller percentage of the body-weight, especially in the smaller rats, than in the normal newborn.

The absolute weight of the fore limbs in the test rats in Group 1 exceeds that of the prenatal controls by 34 per cent (Table 5). In the other groups, however, the difference between the absolute weights of the fore limbs of the test rats and prenatal controls is so irregular that it would be extremely hazardous to draw any conclusions, the average in the test rats being 8 per cent above that of the prenatal controls.

The hind limbs in my prenatal controls form 5.2 per cent, 6.3 per cent, 6.8 per cent, 7.0 per cent, and 7.0 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Therefore, as compared with the normal newborn, the hind limbs in the prenatal controls (fetuses) have a lower relative weight, and as in the case of the fore limbs, this difference in relative weight is most marked in the smaller rats (fetuses) and decreases with the increase in size of the prenatal control (fetus).

In my test rats the hind limbs form 6.7 per cent, 7.5 per cent, 7.4 per cent, 7.9 per cent, and 7.9 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Therefore, in the test rats, the hind limbs form a higher relative percentage of the body-weight than in the prenatal controls. It thus appears that in the test rats the hind limbs are growing faster than the body as a whole.

The absolute weight of the hind limbs in my test rats exceeds that of the prenatal controls in all the groups, being 36.4 per cent, 19.5 per cent, 9 per cent, 13 per cent, and 20 per cent above in Groups, 1, 2, 3, 4 and 5, respectively (Table 5), the average being 19.5 per cent.

It is to be noted that in the prenatal controls the hind limbs, as compared with the fore limbs, have a lower or just equal weight, and the earlier in pregnancy the fetus is removed from the mother the larger are the fore limbs as compared with the hind limbs. This is in accord with the law of cranio-caudal progression in growth as formulated by Jackson (1909). This also may explain the larger size of the hind limbs in the test rats, since in the prenatal controls this growth tendency in the hind limbs has not had sufficient time to develop, due to their shorter sojourn *in utero*, as compared with the test rats, which, although undersized, were born at term.

Jackson and Lowrey (1912), in newborn rats, found the weight of the trunk to be 3.36 gm. In my newborns, the trunk weighs 3.16 gm. and forms 64.4 per cent of the average body-weight, 4.92 gm. In my prenatal controls the trunk forms 65.2 per cent, 64.0 per cent, 63.4 per cent, 65.4 per cent, and 65.3 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the trunk in the prenatal controls is smaller than in the newborn rats. In my test rats the trunk forms 62.7 per cent, 62.3 per cent, 62.3 per cent, 65.5 per cent, and 63.3 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5).

Thus in the test rat the trunk has about the same relative weight as in the newborn rat, while the relative weight is slightly higher in the prenatal controls corresponding to the smaller size of their heads and extremities. The difference in the size of the trunk, however, is slight, as evidenced by the fact that its absolute weight in the test rats shows an average loss of but 1.6 per cent. This loss of weight in the trunk compensates for the larger head and extremities in the tests.

Consequently it appears that in prenatal retardation by inanition there is a slight increase in the weight of the fore limbs especially in the smaller rats, a more marked increase in the hind limbs, and a slight decrease in the weight of the trunk. In postnatal starvation in young rats held at a constant body-weight there was very little change in the weights of the trunk and extremities as compared with controls of the same body-weight. In general, there was a slight increase in the weight of the head, counterbalanced by a slight decrease in the weight of the trunk and extremities (Jackson,[19] 1915; Stewart, 1918). During inanition in adult rats, both the head and extremities appear to increase in relative weight, while the trunk decreases (Jackson,[18] 1915; Table 6).

Integument.—In my normal newborns the average weight of the integument is 0.794 gm. (16.1 per cent of body-weight, 4.92 gm.). Stewart (1919), in new-born litters from the same colony, found the weight of the integument to be 0.754 gm. (15 per cent of the body-weight, 5.03 gm.). These values are slightly lower than that given by Jackson and Lowrey (1912), which was 0.930 gm. (19.8 per cent of body-weight). The difference is probably due to a variation in technic, as it is difficult to remove the skin with uniformity.

In my prenatal controls the weight of the integument forms 11.0 per cent, 12.8 per cent, 13.4 per cent, 13.9 per cent, and 14.2 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus it is evident that the weight of the normal integument is relatively less in the fetus, increasing progressively up to birth.

In my test rats the weight of the integument forms 12.4 per cent, 13.6 per cent, 15.3 per cent, 15.3 per cent, and 14.5 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). The integument in the test rats thus forms a relatively higher percentage of the body-weight, in all the groups, than in the prenatal controls.

The absolute weight (Table 5) of the integument in the test rats exceeds that of the prenatal controls by 18 per cent in Group 1, 6.4 per cent in Group 2, 14.6 per cent in Group 3, 10 per cent in Group 4, and 3 per cent in Group 5. The average increase in all the groups is 10.4 per cent. Although this increase in weight is irregular, it has a downward trend from Group 1 to Group 5 and shows that the nearer the prenatal controls and test rats approach their normal birth-weight, the less is the difference in the relative percentage and absolute weights of their integuments. This increase may be due to the longer interval the test rats remained *in utero* as compared with the prenatal controls, or to the fact that the skin has a stronger growth tendency at this time as compared with some of the other parts of the body. It is interesting to note (Table 6) that Stewart (1918) found the integument to remain at a constant weight in rats starved from birth to three weeks of age, while in older rats starved for longer or shorter periods the loss in weight of the integument was quite marked. In a younger series kept at a maintenance diet from birth to eleven days to twenty-two days, Stewart (1919) found the absolute weight of the integument in the test rats to be 25 per cent above that in the controls of the same body-weight. Jackson[18] (1915) found the integument to lose weight in nearly the same proportion as the whole body in acute and chronic inanition in adult rats.

Skeleton.—As explained under the section on materials and methods, the "moist" skeleton probably corresponds closely to that referred to by Jackson [19](1915) as the cartilaginous skeleton. Since the "gold dust" solution used to rid the skeleton of its ligaments and periosteum acted too strongly on the skeleton in my very small rats, causing a disintegration of the cartilages, no attempts were made to obtain anything corresponding to the cartilaginous skeleton. My observations on the "dried skeleton" are consequently on the dried ligamentous skeleton. Jackson and Lowrey (1912) obtained a value of 0.810 gm. for the ligamentous skeleton in the newborn rats, while in my normal newborn the "moist" skeleton weighs but 0.381 gm., 7.8 per cent of the body-weight, 4.92 gm. However, this agrees very well with the weight of the newborn moist skeleton of 10.377 gm. or 9.0 per cent body-weight, 4.92 gm., given by Conrow (1915). It must be stated, however, that despite the greatest care taken in cleaning the skeletons, their range of weight was very great, even in rats of equal weights (Table 5).

In my prenatal controls, the weight of the moist skeleton forms 7.2 per cent, 7.2 per cent, 7.4 per cent, 7.1 per cent, and 6.7 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the moist skeleton in the prenatal controls has a relative weight slightly below that of the normal newborn rat.

In my test rats the weight of the moist skeleton forms 5.0 per cent, 7.0 per cent, 7.4 per cent, 7.2 per cent, and 7.0 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus there is very little difference in the relative weight of the moist skeleton in the test rats and prenatal controls, except in Group 1, where its relative weight in the test rats is considerably below that of the prenatal controls. This difference is probably due to errors in technic.

By comparing the absolute weights of the moist skeleton in the test rats with the prenatal controls in Table 5, it will be seen that in Group 1 the absolute weight of the moist skeleton in the test rats is 27 per cent less than in the prenatal controls of the same body-weight. Since such a marked difference can not be accounted for by any change in body-length, in fact, the average body-length of the test rats is 7.3 per cent greater than in the prenatal controls of this group, it must be attributed to errors in technic. In the other four groups the difference in the absolute weights of the moist skeleton in the test rats and prenatal controls is very slight and wholly within the limits of error, considering the difficulties of technic. Probably there is very little real difference between the absolute weight of the moist skeleton in test rats and prenatal controls, but one can hardly reach any definite conclusion.

It should be noted, however, that in postnatal inanition the skeleton (undried) shows its greatest increase in weight, 32 per cent, in rats underfed from the age of three weeks to one year (Stewart, 1918). In rats underfed from birth to sixteen days the gain in the skeleton, with musculature, is but 6 per cent (Stewart, 1919). This seems to show that the growth tendency in the skeleton is relatively weak at birth, which may explain its apparent loss of weight in my test rats.

In my normal newborn series the weight of the dried skeleton is 0.089 gm. or 1.8 per cent of the body-weight, 4.92 gm. Conrow (1915) found the dried skeleton to be 1.9 per cent of the body-weight in the normal newborn rat (body-weight, 4.2 gm.; calculated weight of dried skeleton, 0.081 gm.).

In my prenatal controls the weight of the dried skeleton forms 1.4 per cent, 1.5 per cent, 1.5 per cent, 1.7 per cent, and 1.6 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the dried skeleton in the prenatal control has a relative weight slightly below that of the normal newborn rat.

In my test rats the weight of the dried skeleton forms 1.5 per cent, 1.8 per cent, 1.7 per cent, 1.8 per cent, and 1.7 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the dried skeleton in the test rats is slightly higher than in the prenatal controls.

Concerning the absolute weight of the dried skeleton, however (Table 5), the results obtained are different from those in the case of the moist skeleton. Although in Groups 1, 2, and 3 (Table 5) the absolute weights of the moist skeletons in the test rats were 27 per cent, 1.8 per cent, and 5.0 per cent below the prenatal controls of the respective groups, and 0.4 per cent and 0.01 per cent above in Groups 4 and 5, respectively, the absolute weight for the dried skeleton of the test rats exceeds that of the prenatal controls in all five groups, the excess being 7 per cent, 20 per cent, 14 per cent, 9 per cent, and 9 per cent, respectively, from Groups 1 to 5 (Table 5), averaging 12 per cent above for all groups.

This increase in the weight of the dried skeleton in the test rats is evidently due to an increase of dry substance in the bones, cartilages, and ligaments. Therefore, since the dry skeleton shows a relatively greater increase in the test rats as compared with the prenatal controls of the same body-weight, it is apparent that, although the body-weight is retarded, the relative percentages of solid substance and water in the test rats tend to approach that found in the normal newborn rat. The tendency of the skeleton to grow in mass (although at a retarded rate) in cases of underfeeding in rats was observed by Jackson[19] (1915) and by Stewart (1918). Lowrey (1913) found that in the postnatal growth of the rat the amount of dry substance in the ligamentous skeleton increases with age, being 18.1 per cent at birth, 33.3 per cent at twenty days, 39.2 per cent at six weeks, 45.9 per cent at ten weeks, 50.4 per cent at five months, and 52.6 per cent at one year.

No observations were made on any of the skeletons to determine whether there was any variation in the normal process of differentiation (developmental changes) between the test rats and prenatal controls. Jackson[19] (1915) and Stewart (1918), however, found that during maintenance of body-weight by underfeeding in young rats, skeletal growth and differentiation occurred apparently in a normal manner, although at a retarded rate.

Musculature.—The musculature was not weighed separately, but was weighed together with the skeleton and its weight obtained by subtracting the latter from the combined weight. The weight given by Jackson and Lowrey (1912) for the newborn rat is 1.15 gm. or 24 per cent of body-weight, 5.3 gm.; while in my newborns the weight of the musculature was 1.77 gm. or 36 per cent of the body-weight, 4.92 gm. This marked difference is probably due to a variation in technic, as in all my rats the fat was included with the musculature. The reason for this difference in technic is obvious, because in the small rats the fat was poorly differentiated from the muscle.

In my prenatal controls the musculature forms 28 per cent, 32 per cent, 32 per cent, 36.5 per cent, and 37.5 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus in the prenatal controls it is evident that the relative weight of the musculature is less in the smaller rats, increasing progressively up to birth.

In my test rats the musculature forms 28 per cent, 30 per cent, 31 per cent, 33 per cent, and 34 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus, in both the test rats and prenatal controls there is apparently an increasing tendency for the musculature to make up a larger proportion of the body weight as the rat increases in size; that is, the muscle is growing at a relatively faster rate than the remainder of the body, the increase being slightly more marked in the prenatal controls than in the test rats.

The absolute weight of the musculature in the test rats is slightly below that of the prenatal controls with the exception of Group 1 (Table 5), in which its absolute weight in the test rats is 7 per cent above that in the prenatal controls. Taking the groups as a whole, the absolute weight of the musculature in the test rats is but 5 per cent below that in the prenatal controls. This difference is slight, and may in part be due to a decrease in the fat in the test rats. On account of the difficulties encountered in separating the fat from the musculature, they were weighed together, as previously stated.

In postnatal inanition in young rats, there is apparently a slight gain in weight of the musculature. It shows an increase of but 6 per cent, 8 per cent, 10 per cent and 3 per cent, respectively, in rats underfed from birth to sixteen days, from birth to three weeks, from birth to ten weeks, and from three weeks to ten weeks of age (Stewart, 1918, 1919; Jackson,[19] 1915). The greatest gain observed (25 per cent) was in rats underfed from ten weeks to eight months of age (Jackson,[19] 1915). In both acute and chronic inanition in adult rats the musculature loses in about the same proportion as the body as a whole (Jackson, 1915).

In general, it appears that the musculature manifests a relatively weak growth tendency during both prenatal and postnatal inanition, with even a slight loss in the former.

Visceral group.—The visceral group includes the brain, spinal cord, eyeballs, and thyroid, as well as the abdominal and thoracic viscera. Jackson and Lowrey (1912) give the weight of the visceral group in the newborn as 0.954 gm. or 18 per cent of the body-weight, 5.3 gm. Stewart (1919) gives the visceral group a weight of 0.871 gm.; or 17.3 per cent of the body-weight, 5.03 gm. The visceral group in my normal newborn series weighs 0.817 gm. or 16.6 per cent of the body-weight, 4.92 gm.

In my prenatal controls the weight of the visceral group forms 23 per cent, 21 per cent, 18.5 per cent, 19.5 per cent, and 19 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Therefore it is evident that the relative weight of the visceral group in the prenatal controls (fetuses) exceeds that of the normal newborn rat. This difference is most marked in the smaller rats (fetuses), decreasing as the birth-weight is approached, showing that in the fetal life of the rat (from 2 gm. to 4.1 gm.) the viscera constitute a larger proportion of the body-weight than at birth.

In my test rats the weight of the visceral group forms 16.2 per cent, 16.6 per cent, 16.6 per cent, 16.2 per cent, and 15.2 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus, in the test rats the visceral group forms a slightly smaller percentage of the body-weight than in the normal newborn, while in the prenatal controls the converse is true. The relative weight of the visceral group is markedly lower in the test rats than in the prenatal controls.

In my test rats the absolute weight of the visceral group is less than that of the prenatal controls in all the groups (Table 5). In Groups 1 to 5 the absolute weight of the visceral group in the test rats is 27 per cent, 21 per cent, 7 per cent, 17 per cent, and 20 per cent below that of the prenatal controls in the corresponding groups, averaging 18.4 per cent below.

Thus in prenatal inanition the visceral group shows a marked retardation in growth. This is due chiefly to the retarded growth of the liver and lungs.

These results are directly opposed to those in postnatal inanition shortly after birth. Stewart (1918, 1919) found that the absolute weight of the visceral group exceeded that of controls of the same body by 46 per cent, 28 per cent, and 38 per cent in rats underfed from birth to an average of sixteen days, from birth to three weeks of age, and from birth to ten weeks of age, respectively (Table 6). In rats underfed from the age of three weeks to ten weeks and from the age of three weeks to one year, there was no marked change in the weight of the visceral group (Jackson,[19] 1915; Stewart, 1918); while in rats underfed from ten weeks of age to eight months, Jackson[19] (1915) found the weight of the visceral group to be 12 per cent below the normal. He found that the visceral group as a whole undergoes very little change in relative weight in adult rats during either acute or chronic inanition.

From the foregoing data it is evident that the growth tendency of the visceral group in the rat during inanition is relatively weak before birth, strongest shortly after birth, and decreases gradually thereafter.

Remainder.—The "remainder" is obtained by subtracting the weight of the integument, "moist" skeleton, musculature, and viscera from the net body-weight. It thus includes the loss by evaporation of fluids which escape from the body during dissection, also the larynx, trachea, esophagus, salivary and lymph glands, large vessels, and pieces of fat in the omentum. The remainder may vary with the amount of fat removed from different portions of the body.

In general, no attempt was made to remove any of the fat, such as the "nuchal fat pad," retroperitoneal fat, and so forth, all of which was included in the musculature.

In my normal newborns (body-weight 4.92 gm.) the average weight of the remainder was 1.05 gm. (21 per cent of body-weight) Stewart (1919) found its weight to be 1.52 gm. (30 per cent of net body-weight, 5.03 gm.). This weight is considerably higher than mine, probably due to the fact that he included more fat with the remainder than with the musculature. Jackson and Lowrey (1912), however, found its weight to be 0.97 gm. (20.56 per cent of body-weight, 5.3 gm.), a value very close to mine.

In my prenatal controls the weight of the remainder forms 31 per cent, 27 per cent, 28 per cent, 23 per cent, and 23 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the remainder in the smaller prenatal control rats (fetuses) markedly exceeds that of the normal newborn rat, the difference decreasing as the normal birth-weight is approached.

In my test rats the weight of the remainder forms 37 per cent, 34 per cent, 31 per cent, 28 per cent and 30 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Therefore the relative weight of the remainder in the test rats exceeds that of the prenatal controls in all the groups.

The absolute weight of the remainder in my test rats was considerably above that of my prenatal controls in all the groups, the average being 25.4 per cent above (Table 5).

This relative and absolute increase in the remainder is directly opposed to the results obtained in investigations on postnatal starvation (Table 6). In rats held at a constant weight from birth to sixteen days, in another group underfed from birth to three weeks (body-weight 10 gm.), and in another series underfed from birth to ten weeks, Stewart (1918, 1919) found in the remainder a decrease of 59 per cent, 40 per cent, and 23 per cent, respectively, as compared with normal controls of the same body-weight. In rats underfed from the age of three weeks to ten weeks, however, Jackson[19] (1915) found but 2 per cent decrease in the remainder. In young rats underfed up to one year of age he found a decrease of but 5 per cent, while in Stewart's series (1918) there is a decrease of 33 per cent. In acute and chronic inanition in adult rats there is a definite decrease in the weight of the remainder, probably due to a loss of fat (Jackson,[18] 1915).

Why the remainder should decrease during postnatal starvation and increase during prenatal inanition is difficult to explain. Possibly there is a larger amount of circulating fluids, blood, lymph, and so forth, in my test rats than in the prenatal controls. This increase in the remainder evidently compensates for the loss in weight of the visceral group. This is the converse of what occurs in postnatal starvation, as found by Stewart (1919) in the rats held at birth-weight.

Brain.—In my normal newborns the average weight of the brain is 0.235 gm. (4.8 per cent of the body-weight, 4.92 gm.). Stewart (1919) gives the weight of the brain in the newborn as 0.224 gm. (4.5 per cent of the body-weight, 5.03 gm.). Jackson (1913) found the weight of the brain in the newborn rat to be 4.8 per cent of the gross body-weight.

In my prenatal controls the weight of the brain forms 6.2 per cent, 5.6 per cent, 5.0 per cent, 4.8 per cent, and 4.4 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus in the prenatal controls the relative weight of the brain in the smaller rats (fetuses) is greater than that of the normal newborn, this difference in relative weight decreasing, however, as the birth-weight is approached.

In my test rats the weight of the brain forms 6.6 per cent, 6.2 per cent, 5.6 per cent, 5.3 per cent and 5.0 per cent of the body-weight in

Groups 1 to 5. respectively (computed from Table 5). Thus, in the test rats the brain forms a slightly higher per cent of the body-weight than in the prenatal controls; in both, the smaller the rat, the greater is the weight of the brain relative to the body-weight. Since in the test rats, especially in the smaller ones, the brain tends to form a relatively larger part of the body-weight than in either the normal newborns or in the prenatal controls, it may be quite safely assumed that in a state of inanition of the mother the brain of the fetus has a greater growth tendency than does the remainder of the body as a whole.

In the test rats the absolute weight of the brain exceeds by 12 per cent to 13 per cent (average 12.5 per cent) that in the corresponding prenatal norms, constantly throughout all the groups (Table 5).

Comparing these results with those obtained in postnatal inanition by Jackson and Stewart (Table 6), it is seen that the brain shows its greatest tendency to increase in weight in rats underfed from birth to sixteen days (Stewart, 1919). Here the brain shows a gain of 125 per cent in absolute weight above controls of the same body-weight. This gain drops to 60 per cent in rats (body-weight 10 gm.) underfed from birth to three weeks (Stewart, 1918); and in rats starved from birth to ten weeks the gain is but 8 per cent. In rats underfed from three weeks after birth to ten weeks of age the brain shows little or no change (Jackson,[19] 1915).

Hatai (1904) found a decrease of 5 per cent in the absolute weight of the brain in young rats losing 30 per cent of their body-weight on an unfavorable diet of starch and beef fat. Later (1908) he found no change in the brain-weight in rats stunted on an unfavorable diet, as compared with normal rats of the same body-weight.

Donaldson (1911), in young rats held at maintenance from thirty days to fifty-one days of age, found the brain-weight to average 7 per cent less than in normal controls of the same age. If a comparison is made, however, with the calculated initial brain-weight, as he points out, the average weight of the brain is 3.6 per cent greater in the underfed rats.

In adult rats, during both acute and chronic inanition, Jackson[18] (1915) observed that the brain even loses slightly in weight.

From the foregoing results, it may be assumed that in the rat during inanition the brain possesses its strongest growth tendency at birth and that this tendency decreases with age (Table 6). Whether this growth impulse is stronger or weaker before birth is hard to decide. From a comparison of the data it would seem to be weaker before birth, since in my test rats from underfed mothers the weight of the absolute brain increased but 12.5 per cent above that of the prenatal norms, while Stewart (1918*a*), in starvation seventeen days to twenty-two days after birth, found the absolute weight of the brain to gain 125 per cent above that of the controls of the same body-weight. It must be remarked, however, that in my tests the exact character and extent of the inanition of the fetus are somewhat uncertain.

Spinal cord. —In my normal newborns the spinal cord weighs 0.036 gm. (0.71 per cent of the body-weight, 4.92 gm.). Stewart (1919) gives the weight of the spinal cord in the newborn as 0.035 gm. (0.70 per cent of the body-weight, 5.0 gm.). The Wistar norm (Donaldson, 1915) for the spinal-cord weight is 0.034 gm. at body-weight of 4.95 gm.

The weight of the spinal cord in my prenatal controls forms 1.12, per cent, 1.00 per cent, 0.91 per cent, 0.83 per cent, and 0.75 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus it is evident that the spinal cord, similar to the brain, in the prenatal controls has a higher relative weight than in the normal newborn rat.

In my test rats the weight of the spinal cord forms 1.13 per cent, 1.01 per cent, 0.86 per cent, 0.80 per cent, and 0.75 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5).

Thus, in the smaller rats, both the test rats and prenatal controls, as compared to the normal newborns, the spinal cord forms a relatively higher percentage of the body-weight, this tendency lessening with the increase in the size of the rats, until in the larger rats this difference in relative weight disappears.

From the data in Table 5, the absolute weight of the spinal cord is lower in the test rats than in the prenatal controls, with the exception of Groups 1 and 2, where it is respectively 6 per cent and 2 per cent higher in the test rats. The absolute weight in all the groups averages but 0.26 per cent higher in the prenatal controls than in the test rats. This is such a slight difference that it might very well be attributed to errors in technic, since it is difficult to remove the cord intact from these small rats and also to sever the head from the trunk at exactly the same place. Probably there is very little change in the spinal cord of the fetus during inanition in the mother. The fact that the body-length in the tests and controls varies but little, 1 per cent higher in the test rats, would lead one to expect but little difference in the corresponding weights of the spinal cord.

The results obtained in postnatal inanition, however, might lead one to expect an increase in the size of the cord in the stunted individual. Bechterew (1895), in acute inanition of puppies and kittens, made a study of the central nervous system after death of the animal and found the least loss in the spinal cord. Donaldson (1911) found a slight increase in the weight of the spinal cord in young rats, held at body-weight of 34 gm. from thirty days to fifty-one days of age. Jackson (1915) found no change in the weight of the spinal cord in acute inanition in adult rats, while in chronic inanition in adult rats he found a slight decrease in the weight.

In newborn rats, however, Stewart (1919) noted a marked tendency for the cord to continue growing during inanition in which the body is kept at nearly constant weight. From the data in Table 6, it is evident in underfed young rats that the spinal cord possesses a very strong growth tendency, greatest at or shortly after birth, but also present up to adult life. It should be noted that this growth tendency persists for a longer time in the cord than in the brain, probably due to the fact that the brain normally completes its postnatal growth at a relatively earlier age than does the cord.

Why the cord should lose while the brain gains in weight during fetal inanition is difficult to explain. So far as their normal growth tendency during the fetal period is concerned, both appear to be decreasing in about the same relative proportion, judging from a comparison of their prenatal growth norms.

Eyeballs.—The eyeballs in my normal newborns weigh 0.025 gm. and form 0.50 per cent of the body-weight, 4.92 gm. In Stewart's (1919) newborn they weighed 0.0235 gm. and formed 0.47 per cent of the body-weight, 5.03 gm. Jackson (1913) gives the weight of the eyeballs in the newborn as 0.025 gm. and 0.53 per cent of the body-weight.

In my prenatal controls the eyeballs form 0.38 per cent, 0.42 per cent, 0.42 per cent, 0.38 per cent, and 0.37 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Compared with the normal newborn rat, the relative weight of the eyeballs is much lower in the prenatal controls.

In my test rats the eyeballs form 0.57 per cent, 0.52 per cent, 0.50 per cent, 0.48 per cent, and 0.46 per cent of the body-weight in

Groups 1 to 5, respectively (computed from Table 5). Thus it is evident that the eyeballs in the test rats have a much higher relative weight than in the prenatal controls. In the test rats the relative weight of the eyeballs is about the same as that of the normal newborn. (In the smaller rats it is slightly higher.)

The absolute weight of the eyeballs is markedly higher in the test rats than in the controls in all the groups (Table 5), being most pronounced in Group 1 (the smallest rats), in which the average absolute weight of the eyeballs of the test rats is 56 per cent above that in the prenatal controls. It is interesting to note that, in the range of their weights, in Group 1 the heaviest eyeballs in the prenatal control just equal the lightest in the test rats. In the other groups the eyeballs in the test rats show an increase in absolute weight above the prenatal controls of over 20 per cent. The average total excess of the absolute weight of the eyeballs in the test rats above that in the prenatal controls is 31.4 per cent.

These results are quite in accord with those obtained in postnatal inanition, although less marked. In postnatal inanition the strongest growth capacity of the eyeball is exhibited in newborns underfed from birth to an average of sixteen days (Stewart, 1919), the increase being 146 per cent (Table 6). This growth capacity of the eyeball during inanition then decreases somewhat, but rises again in older rats and persists in animals underfed up to one year of age. In older rats (adults), in both acute and chronic inanition, the eyeballs lose slightly in weight according to Jackson (1915). He suggests that this remarkable capacity of the eyeball to continue its growth during inanition may be due to its power to absorb water, which makes up so large a proportion of its composition.

Thymus.—In my normal newborns, the average weight of the thymus is 0.0070 gm. or 0.14 per cent of the body-weight, 4.92 gm. Stewart (1919) gives the weight of the thymus in the newborn as 0.0079 gm. or 0.15 per cent of the body-weight—5.03 gm. The Wistar norm (Donaldson, 1915) is 0.0080 gm., body-weight, 4.9 gm.

In my prenatal controls the thymus forms 0.11 per cent, 0.13 per cent, 0.13 per cent, 0.13 per cent, and 0.12 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the thymus in the prenatal controls is slightly lower than in the normal newborn rat.

In my test rats the thymus forms 0.08 per cent, 0.09 per cent, 0.11 per cent, 0.11 per cent, and 0.10 per cent of the body weight in Groups 1 to 5, respectively (computed from Table 5). Thus the thymus forms a much smaller part of the body-weight in the test rats than in the prenatal controls; that is, its growth has been retarded in the test rats. This is more clearly brought out by a comparison of the absolute weights. In Group 1 the absolute weight of the thymus, in the test rats, is 29 per cent below that of the prenatal controls; in Group 2, 33 per cent below; in Group 3, 12 per cent below; in Group 4, 16 per cent below; and, in Group 5, 15 per cent below, averaging 21 per cent below for all groups. Thus it is seen that the growth of the thymus is considerably retarded in the rat fetus during inanition of the mother.

These results also agree with the loss of weight (hunger involution) of the thymus in cases of postnatal inanition. Jonson (1909), in young rabbits, kept at constant body-weight by underfeeding for four weeks, found the weight of the thymus to be reduced to one-thirtieth of that in the controls, the greatest loss of weight being in the cortex. He also found that the reduction in weight of the thymus was proportionate to the loss of the body-fat. This reduction in weight of the thymus in rabbits is much more marked than that obtained by Jackson and Stewart on rats. Jackson[19] (1915) found a loss of 90 per cent in the thymus in young rats held at maintenance from the age of three weeks to ten weeks and also in young rats underfed ten weeks to eight months. Stewart (1918 and 1919) found losses of 80 per cent, 30 per cent, and 49 per cent, respectively, in the weights of the thymus in young rats underfed from birth to ten weeks, from birth to three weeks, and held at birth-weight for sixteen days. Jackson[18] (1915) found no marked change in the weight of the thymus in cases of acute and chronic inanition in adult rats, at which age involution of the thymus had already occurred. The thymus normally reaches its maximum absolute weight in the rat at eighty-five days (Hatai, 1914) and at one year it has undergone a complete age involution (Jackson, 1913).

Heart.—In my normal newborns, the average weight of the heart is 0.027 gm. or 0.55 per cent of the body-weight, 4.92 gm. Jackson (1913) gives its weight in the newborn as 0.030 gm. or 0.65 per cent of the body-weight, 5.08 gm. Stewart (1918*a*) gives a weight of 0.031 gm., or 0.61 per cent of the body-weight, 5.03 gm.

In my prenatal controls the weight of the heart forms 0.49 per cent, 0.52 per cent, 0.49 per cent, 0.50 per cent, and 0.44 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the heart in the prenatal controls is considerably less than in the normal newborn rat.

In my test rats the weight of the heart forms 0.55 per cent, 0.53 per cent, 0.54 per cent, 0.53 per cent and 0.49 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the heart in the test rats is slightly higher than in the prenatal controls. The relative weight in both the test rats and prenatal controls is less than that in the normal newborn rats. It is also evident that in both the prenatal controls and test rats the relative weight of the heart is greater in the smaller as compared with the larger rats.

The absolute weight of the heart is constantly higher in the test rats than in the prenatal controls, the difference being most marked in Group 1 (Table 5) in which the heart weight in the test is 17 per cent higher than that in the prenatal controls. This difference, however, is not so pronounced in the other groups, averaging for all groups 8 per cent above in the test rats.

This gain in heart-weight in prenatal starvation agrees with the results of Stewart (1919), who noted a gain of 26 per cent in absolute weight of the heart in test rats kept at a birth-weight of about 5 gm. for an average of sixteen days. However, in another series (Stewart, 1918) starved from birth to three weeks (body-weight 10 gm.), the heart showed a loss of 5 per cent. In still another group, underfed from birth to ten weeks (body-weight 24 gm.), Stewart (1918) found a gain of 27 per cent in the weight of the heart. In slightly older rats, underfed for various periods, the heart loses slightly (Jackson,[19] 1915; Stewart, 1918), while in adult rats the heart shows a decided loss in both acute and chronic inanition (Jackson, 1915).

Lungs.—Jackson (1913) gives the absolute weight of the lungs as 0.078 gm. or 1.6 per cent of the body-weight, 5.1 gm. The Wistar norm (Donaldson, 1915) is 0.079 gm., or 1.6 per cent of the body-weight, 4.9 gm. In my newborn controls the weight of the lungs is 0.073 gm., or 1.5 per cent of the body-weight, 4.92 gm.

In my prenatal controls the lungs form 2.8 per cent, 2.7 per cent, 2.3 per cent, 2.0 per cent and 2.1 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the lungs is markedly higher in the prenatal controls than in the normal newborn rats. This difference in relative weight is greatest in the smaller rats and decreases as the birth-weight is approached.

In my test rats the lungs form 1.2 per cent, 1.5 per cent, 1.4 per cent, 1.5 per cent and 1.3 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus, in the test rats the lungs have a relative weight which is about that of the normal newborn rat, whereas in the prenatal controls the relative weight is approximately double that at birth.

The absolute weight of the lungs in the test rats is 54 per cent, 44 per cent, 40 per cent, 23 per cent and 36 per cent below that of the prenatal controls in Groups 1 to 5, respectively, averaging 39.4 per cent below for all groups. It is interesting to note that in the range of the individual weights the largest lungs in the test rats about equal in size the smallest in the controls.

This lack of ability of the lungs to grow, manifested by a subnormal weight during prenatal inanition, agrees with the results obtained in the postnatal starvation experiments (Table 6). Stewart (1919) found a slight gain (3 per cent) in the lungs of rats underfed from birth to an average of sixteen days. On underfeeding from birth to three weeks, and from birth to ten weeks of age, the lungs showed a loss of 26 per cent in both series (Stewart, 1918). Jackson[19] (1915) found that the lungs lose 15 per cent in rats starved from the age of three weeks to ten weeks. He also found a loss of 13 per cent in the lungs in a group underfed between the ages of ten weeks and eight months. Stewart (1918), however, found the lungs in rats underfed from an age of three weeks to one year to gain in weight 28 per cent (probably pathologic). Jackson[18] (1915) found that the lungs show a tendency to lose weight in adult rats in both acute and chronic inanition and that this loss of weight is about in proportion to the loss of the body as a whole. Consequently, it may be concluded that the lungs exhibit a very weak growth tendency during prenatal as well as during postnatal conditions of inanition.

Liver.—The Wistar norm (Donaldson, 1915) for the liver of the newborn rat is 0.205 gm., with a body-weight of 4.9 gm. Stewart (1919) gives the weight as 0.245 gm. or 4.9 per cent of the body-weight, 5.03 gm. Jackson (1913) finds a weight of 0.230 gm. or 4.3 per cent of the body-weight. In my newborns the weight of the liver is 0.250 gm. or 5.1 per cent of the body-weight, 4.92 gm.

In my prenatal controls the liver forms 9.1 per cent, 8.7 per cent, 7.8 per cent, 8.1 per cent and 7.7 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the liver in the prenatal controls markedly exceeds that of the normal newborn rat. This difference in relative weight decreases, however, as the normal birth-weight is approached.

In my test rats the liver forms 4.1 per cent, 4.5 per cent, 4.6 per cent, 4.9 per cent, and 4.4 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). In the smaller test rats, the liver forms a relatively smaller precentage of the body-weight than in the normal newborns. In the prenantal controls, however, the liver forms a much higher relative percentage of the body-weight than in either the normal newborns or in the test rats.

In the test rats the absolute weight of the liver is markedly subnormal in all the groups (Table 5), averaging 45 per cent below that of the prenatal controls In the range of the individual weights in the same groups the highest weight for the liver in the test rats is much below the lowest weight in the prenatal control. Thus in prenatal inanition the growth of the liver is markedly retarded, reaching an absolute weight of approximately one-half that of the prenatal controls.

In postnatal inanition, Stewart (1919) found that the liver loses 23 per cent in rats held at a constant weight from birth to an average of sixteen days (Table 6). In two other groups underfed from birth to three weeks, and from birth to ten weeks, he found that the liver gains in weight 17 per cent and 64 per cent, respectively. Jackson[19] (1915), in young rats underfed from the age of three weeks to ten weeks, found a gain of 10 per cent in the liver-weight. In rats starved for a longer period, or where it was begun later, the liver shows a loss of weight (Jackson,[19] 1915; Stewart, 1918). Jackson[18] (1915) found that the liver loses markedly in cases of acute and chronic inanition in adult rats.

Thus it would seem that in prenatal life and for a period up to several days after birth, the liver during inanition has a very weak growth tendency, which becomes stronger after the first week of postnatal life and persists up to six weeks or two months of age, then decreases until it is very weak again as the adult stage is approached.

Spleen.—The Wistar norm (Donaldson, 1915) for the spleen in the newborn rat is 0.008 for a body-weight of 4.9 gm. Jackson (1913) gives the weight of the spleen as 0.010 gm., or 0.22 per cent of the body-weight. Stewart (1919) finds the weight to be 0.011 gm., or

0.22 per cent of the body-weight, 5.03 gm. In my normal newborns the average weight of the spleen is 0.010 gm., or 0.20 per cent of the body-weight, 4.92 gm.

The spleen in the prenatal controls forms 0.08 per cent, 0.08 per cent, 0.13 per cent, 0.14 per cent, and 0.15 per cent of the body-weight in Groups 1 to 5, respectively, while in the test rats in the corresponding groups it forms 0.12 per cent, 0.12 per cent, 0.16 per cent, 0.17 per cent, and 0.21 per cent of the body-weight (computed from Table 5). Thus the spleen in the prenatal controls forms a much smaller proportion of the body-weight than it does in the normal newborn; that is, in the rat fetus the spleen is at first relatively small (0.08 per cent of body-weight in a 2.19-gm. fetus), but gradually increases in size up to shortly before birth (0.15 per cent of the body weight in a 4.19-gm. fetus), when, in order to reach its normal relative percentage of the newborn body weight, it must increase rapidly in size (an increase from 0.15 per cent to 0.22 per cent of the body-weight while the fetus is growing from 4.19 gm. to 5.0 gm.).

Jackson (1909) in referring to the human fetus says:

> "The spleen is at first relatively small, but increases slowly to an average of 0.176 per cent of the whole body in the seventh month. About this time it appears to increase rapidly in relative size, averaging over 0.4 per cent in the eighth and ninth months. In the full-term still-born (143 cases) the spleen averages 0.32 per cent of the total body-weight, and in the live-born (101 cases) 0.43 per cent."

Lowrey (1911) finds practically the same course of growth in the spleen of the pig fetus.

Thus it appears that the prenatal growth of the spleen in the rat is similar to that observed in the human and the pig. In all three animals the spleen apparently develops a strong growth tendency shortly before birth. This probably explains the increase in the relative weight of the spleen in the test rats. Since the test rats have a longer time in the uterus, this late growth tendency in the spleen has more opportunity to develop than in the prenatal controls.

The absolute weight of the spleen in the test rats is constantly higher than that in the prenatal controls in all the groups (Table 5), averaging 34 per cent above.

This growth of the spleen during prenatal inanition agrees very well with the results obtained during postnatal starvation. Stewart (1919) found the spleen to gain 38 per cent in rats kept at birth-weight for an average of sixteen days of age. In another series (Stewart,

1918) underfed from birth to three weeks of age, the spleen lost 49 per cent. In a third series, starved from birth to ten weeks of age, the spleen gained 24 per cent. Jackson[19] (1915) found the spleen to lose 42 per cent in rats starved from three weeks of age to ten weeks. In two series starved during later periods (Jackson,[19] 1915; Stewart, 1918) there was no material change in its weight.

In adult rats in chronic inanition the reduction in the weight of the spleen is about the same as that for the whole body, while in acute inanition the loss is much greater (Jackson,[18] 1915).

Intestines.—The intestines, with their contents, have an average weight of 0.141 gm. and form 3.0 per cent of the body-weight (4.92 gm.) in my normal newborns. The empty intestines have an average weight of 0.062 gm. or 1.3 per cent of the body-weight.

In my prenatal controls the intestines with contents form 1.6 per cent, 1.9 per cent, 1.9 per cent, 2.4 per cent, and 2.3 per cent of the body-weight (computed from Table 5). Thus the relative weight of the intestines with contents is considerably less in the prenatal controls than in the normal newborn rat, the difference decreasing, however, as the prenatal control fetuses approach their birth-weight.

In my test rats the intestines with contents form 1.8 per cent 2.2 per cent, 2.5 per cent, 2.4 per cent, and 2.4 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the intestines with contents is slightly higher in the test rats than in the prenatal controls.

The empty intestines in my prenatal controls form 0.64 per cent, 0.75 per cent, 0.76 per cent, 0.93 per cent, and 1.60 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus it is evident that the relative weight of the empty intestines is lower in the fetus, increasing progressively up to birth.

In my test rats the empty intestines form 0.60 per cent, 0.71 per cent, 0.95 per cent, 0.82 per cent, and 0.90 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Therefore the relative weight of the empty intestines in the test rats is slightly less than that of the prenatal controls.

The absolute weight of the intestines with contents, in the test rats, exceeds that of the prenatal controls in Groups 1, 2, 3, and 5 by 24 per cent, 17 per cent, 31 per cent, and 2 per cent, respectively. In Group 4 the absolute weight is 0.06 per cent lower in the test rats. From the foregoing it is evident that the intestinal contents in the smaller test rats markedly exceeds that of the smaller prenatal controls (fetuses), this difference disappearing in the larger rats, that is, as the normal birth-weight is approached.

The absolute weight of the empty intestines, however, in the test rats of Groups 1 and 2 is below that of the prenatal controls, 3 per cent and 5 per cent, respectively. In Group 3 in the test rats it is 27 per cent above, and in Groups 4 and 5 it is 12 per cent and 16 per cent respectively below that of the controls; averaging 2 per cent below in the test rats for all groups. This difference in absolute weight is slight and may be due to the difficulty of removing the intestinal contents in a uniform manner. It is difficult to explain on any other premises why the absolute weight of the intestines with contents in the test rats should exceed that of the controls by 15 per cent while below them 2 per cent in absolute weight when empty. Jackson[19] (1915), however, in underfed young rats, found an increase in the intestinal contents, while the empty intestines lost in weight. Since the full stomach in my test rats weighs 3.7 per cent less than that of the prenatal controls, there may be a passage of stomach contents into the intestines, with a possible increase of meconium and mucus in the older rats (test), which may account for the increase in the absolute weight of the full intestines in the test rats.

There may be a retardation of the growth of the intestines during prenatal inanition while the stomach increases slightly in weight. However, on account of the irregularities of the results obtained, it would be hazardous to venture any definite conclusion.

It has been found, however, that in postnatal inanition the gastro-intestinal tract taken as a whole manifests a marked growth capacity in rats starved shortly after birth. Stewart (1919) found that the intestines gained 40 per cent in weight in rats kept at a constant birth-weight for an average of sixteen days. In two other groups, underfed from birth to three weeks of age and from birth to ten weeks of age, Stewart (1918) found that the gastro-intestinal tract gained 17 per cent, and 100 per cent, respectively.

Jackson[19] (1915) also found that the gastro-intestinal tract gained 28 per cent in rats underfed from the age of three weeks to ten weeks. However, in cases of chronic inanition in rats underfed from the age of three weeks to one year (Stewart, 1918) and from the age of ten weeks to eight months (Jackson[19], 1915), there is a loss in the gastro-intestinal tract of 27 per cent and 26 per cent, respectively.

In adult rats, during both acute and chronic inanition, there is a marked decrease in the gastro-intestinal tract, both filled and empty, the loss being about 57 per cent in each group (Jackson,[18] 1915).

Stomach.—As described under the section on materials and methods, the stomach in the test rats and controls was weighed as a separate organ, instead of being included with the intestines and pancreas as the gastro-intestinal group. However, the stomach and intestines were removed and weighed full, and empty, in a group of four normal newborn rats (average body-weight 5.0 gm.). The average weight of the stomach and intestines with their contents was 0.317 gm. Their weight, empty, was 0.128 gm., a value which agrees very well with that of Jackson (1913), who gives their weights with and without contents as 0.297 gm. and 0.117 gm. respectively.

The full stomach in my normal newborns had an average weight of 0.1198 gm. (2.4 per cent of body-weight 4.92 gm.). The empty stomach weighed 0.020 gm. or 0.41 per cent of the body-weight. Hatai (1918) gives the weight of the empty stomach as 0.030 gm. or 0.70 per cent of the body-weight, 4.2 gm. This value is considerably higher than mine, probably due to a variation in technic.

In my prenatal controls, the full stomach forms 0.7 per cent, 1.5 per cent, 1.5 per cent, 1.2 per cent, and 1.8 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the full stomach in the prenatal controls is much less than that in the normal newborn rat. The small relative weight of the full stomach in Group 1 agrees with the observations of Jackson (1909) that in the human fetus the relative weight of the stomach with contents is at first but little larger than that for the empty stomach.

The full stomach in my test rats forms 1.9 per cent, 1.5 per cent, 1.5 per cent, 1.3 per cent, and 1.0 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the full stomach is greater in the smaller test rats, while the converse is true of the prenatal controls.

The absolute weight of the full stomach is variable, averaging 3.7 per cent less in the test rats than in prenatal controls (Table 5).

The empty stomach in my prenatal controls forms 0.31 per cent, 0.37 per cent, 0.39 per cent, 0.37 per cent, and 0.38 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the empty stomach in the prenatal controls is slightly less than that of the normal newborn rat, the difference in relative weight being most marked in Group 1.

In my test rats the empty stomach forms 0.34, per cent, 0.38 per cent, 0.40 per cent, 0.38 per cent, and 0.39 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus, with the exception of Group 1, there is very little difference in the relative weight of the stomach in the test rats and in the prenatal controls.

In the largest rats (Group 5) the stomachs, in both the test rats and prenatal controls, has practically the same relative weight as in the normal newborn rats. Thus the normal relative weight of the stomach is disturbed very little by prenatal inanition. The stomach in the test rats shows an average of 5.6 per cent in absolute weight above the prenatal norms. The difference is most marked in Group 1 (the smallest rats), where the absolute weight in the test rats is 15 per cent above that of the controls (Table 5).

Pancreas.—In postnatal inanition experiments on rats no direct observations have heretofore been made on the weight of the pancreas Therefore no comparisons can be made with postnatal results.

Hatai (1918) gives the weight of the pancreas in the new born rat as 0.0193 gm., or 0.45 per cent body-weight, 4.25 gm. In my normal newborns the weight of the pancreas is 0.0224 gm., or 0.45 per cent body-weight, 4.92 gm.

In my prenatal controls the weight of the pancreas forms 0.35 per cent, 0.38 per cent, 0.35 per cent, 0.45 per cent, and 0.42 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5) Thus, in the smaller prenatal controls (fetuses) the pancreas has a lower relative weight than in the larger rats (fetuses) in which the pancreas has approximately the same relative weight as in the normal newborn rat.

In my test rats the average weight of the pancreas forms 0.31 per cent, 0.37 per cent, 0.42 per cent, 0.37 per cent, and 0.46 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus in the test rats, as in the prenatal controls, the pancreas in the smaller rats forms a lower percentage of body-weight than in the larger rats, in which the pancreas has a relative percentage weight about the same as that in the normal newborn rat, but the weight of the pancreas is extremely variable in its individual weight and average absolute weight throughout all the groups (Table 5).

In Group 1 the absolute weight of the pancreas in the test rats is less by 10 per cent than in the prenatal controls; in Group 2 it is 2 per cent less; in Group 3 it is 20 per cent heavier; in Group 4, 16 per cent lighter; while in Group 5 it is 9 per cent heavier. The average for all groups shows a deficit of 0.2 per cent in the test rats. From this it is seen that the weight of the pancreas is variable. Its low weight in one group is balanced by its high weight in another. Prenatal inanition probably has very little effect on the relative weight of the pancreas, as its average weight in the test rats is but 0.2 per cent below that in the prenatal norms for the various groups.

Suprarenals.—The weight of the suprarenals, according to the Wistar norm (Donaldson, 1915), is 0.0017 gm. for a rat of 5.1 gm., or 0.034 per cent of the body-weight. Jackson (1913) gives the weight of the suprarenals in the newborn as 0.0019 gm. (0.00188), or 0.039 per cent of the body-weight. In my normal newborns the weight of the suprarenals averages 0.0016 gm. or 0.032 per cent of the body-weight, 4.92 gm.

The weight of the suprarenals in my prenatal controls forms 0.044 per cent, 0.050 per cent, 0.048 per cent, 0.049 per cent, and 0.045 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the suprarenals in the prenatal controls markedly exceeds that of the normal newborn rat.

In my test rats the average weight of the suprarenals forms 0.026 per cent, 0.023 per cent, 0.022 per cent, 0.024 per cent, and 0.024 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus it is evident that the relative weight of the suprarenals in the test rats is less than one-half that in the prenatal controls. On the other hand, however, their relative weight in the prenatal controls greatly exceeds their relative weight at birth. Thus, in the prenatal norm fetuses studied (2.19 gm. to 4.19 gm.), the suprarenals are relatively larger than at birth. They are probably still larger, relatively, in earlier stages, although no data from their earlier size in the rat are available. Jackson (1909) found that in the human fetus the suprarenals increase rapidly to their maximum (relative volume) in the third fetal month, after which they decrease steadily in relative size.

In the test rats the suprarenals show an average weight 52 per cent below that of the prenatal controls (Table 5). The excessively weak growth-tendency of the suprarenals during fetal inanition can not be explained as due to any peculiarity of their normal growth in rats at this time, for, as shown above, the prenatal controls maintain a nearly constant relative (percentage) weight during this period.

In postnatal inanition Stewart (1919) found that in rats kept at birth-weight for 16 days the suprarenals gained 5 per cent in absolute weight over newborn controls, but with longer periods of starvation (underfed from birth to three weeks, body weight 10 gm.), he found that the suprarenals increased markedly in weight (60 per cent and 114 per cent, respectively).

Jackson[19] (1915) also found that the suprarenals manifested a marked growth-tendency in young rats underfed from the age of three weeks to ten weeks, the suprarenals gaining 26 per cent. Stewart (1918), in chronic inanition in young rats, found that the suprarenals gained 48 per cent in absolute weight, while Jackson[19] (1915) found that the suprarenals lost during chronic inanition (26 per cent). In adult rats there is very little or no loss of absolute weight of the suprarenals during either acute or chronic inanition (Jackson,[18] 1915).

From these observations it would appear that the suprarenals in the rat have a weak growth-tendency during inanition in prenatal life and that it is still slight up to sixteen days of age, reaching its maximum at a period between this time and ten weeks, and declining thereafter.

Kidneys.—Jackson (1913) found the kidneys in the newborn rat to weigh 0.46 gm. or 0.97 per cent of the body-weight. The Wistar norm (Donaldson, 1915) for the kidneys in the newborn is 0.48 gm., or 0.97 per cent of the body-weight, 4.95 gm.; in my normal newborns the weight of the kidneys is 0.46 gm. or 0.94 per cent of the body-weight, 4.92 gm.

In my prenatal controls the weight of the kidneys forms 0.58 per cent, 0.63 per cent, 0.54 per cent, 0.71 per cent and 0.70 per cent of the body-weight in Groups 1 to 5 respectively (computed from Table 5). Thus in the prenatal controls the relative weight of the kidneys is less than that in the normal newborn rats. The difference decreases, however, from the small to the larger rats (fetuses). Therefore it is evident that in the rat fetus (from 2 gm. to 4.1 gm.) the kidneys are growing faster than the body as a whole.

In my test rats the average weight of the kidneys forms 0.56 per cent, 0.67 per cent, 0.69 per cent, 0.67 per cent, and 0.71 per cent of the body-weight in Groups 1 to 5 respectively (computed from Table 5). There is very little difference in the relative weight of the kidneys in the test rats and the prenatal controls, but in neither have the kidneys reached the relative (percentage) weight of the body which is normal at birth. In both, the kidneys are growing faster than the body as a whole.

The absolute weight of the kidney is variable. Comparing the test rats and the prenatal controls (Table 5), it is seen that in some groups the absolute weight is higher in the test rats, in others in the prenatal controls. This makes the results seem of questionable significance. This variability can not be attributed to errors in technic, however, as the kidney is an organ easy to remove and clean. In the test rats the absolute weight of the kidneys shows an average weight of 6 per cent above the prenatal controls.

This increase of 6 per cent in the absolute weight of the kidney during prenatal inanition is not nearly so marked as that noted in young rats underfed for various periods after birth. Stewart (Table 6) found that the kidneys showed a gain of 90 per cent in absolute weight in rats kept at a birth-weight for an average of sixteen days; this gain was less marked if the underfeeding was prolonged to three weeks, being 21 per cent (Stewart, 1918). In rats underfed from birth to ten weeks the kidneys showed a gain of 38 per cent. In rats underfed from the age of three weeks to ten weeks, however, Jackson[19] (1915) found that the kidneys increased but 4 per cent; and in chronic inanition in young rats, where the starvation was begun from three weeks to ten weeks after birth and continued to eight months or one year (Jackson,[19] 1915; Stewart, 1918), the kidneys showed a slight loss in weight.

In both acute and chronic inanition in adult rats the kidneys lose in weight relatively slightly less than the body as a whole (Jackson,[18] 1915).

Testes and epididymides.—The Wistar norm (Donaldson, 1915) for the weight of the testes in the newborn rat is 0.004 gm. or 0.081 per cent of the body-weight, 4.9 gm. Stewart (1919) gives the weight of the testes in the newborn as 0.0027 gm., or 0.053 per cent of the body-weight, 5.08 gm. In my normal newborn the average weight of the testes is 0.0029 gm., or 0.060 per cent of the body-weight, 4.92 gm. There are no prenatal control males in Group 1, consequently no testes for comparison.

In my prenatal controls the weight of the testes forms 0.050 per cent, 0.047 per cent, 0.042, per cent and 0.040 per cent of the body in

Groups 2 to 5, respectively (computed from Table 5). Thus the relative weight of the testes in the prenatal controls is considerably less than that in the newborn rat. It is to be noted that the relative weight is higher in the smaller rats and decreases as the birth-weight is approached. That is, the testes are lagging behind the body-growth as a whole. In order to reach the relative weight normal for the testes at birth, there must necessarily be a period of very active growth in the testes just before birth, in fetuses between the body-weights of 4.1 gm. and 5 gm.

In my test rats the average weight of the testes forms 0.030 per cent, 0.052 per cent, 0.056 per cent, 0.048 per cent, and 0.050 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus the relative weight of the testes is slightly higher in the test rats than in the prenatal controls. In both, however, the relative weight of the testes is markedly below that in the normal newborn rat.

The absolute weight of the testes in the test rats averages 16 per cent above the prenatal controls, in four groups.

In postnatal starvation, the testes during the first weeks of life manifest a remarkable growth tendency. Stewart (1919) found that the absolute weight of the testes in rats kept at a constant birth-weight for sixteen days exceeded that of newborn controls by 374 per cent (Table 6), which was the strongest growth tendency exhibited by any organ in the body. In rats underfed from birth to three weeks. the increase in the absolute weight of the testes above that of controls of the same body-weight, 10 gm., is less, being 188 per cent (Stewart, 1918). In a longer period of underfeeding, birth to ten weeks, the testes show a gain in weight of but 51 per cent (Stewart, 1918); while in underfeeding from three weeks of age to ten weeks the testes gain 34 per cent (Jackson,[19] 1915). With prolonged starvation, however, the testes may lose considerably (Stewart, 1918), or may show practically no change (Jackson,[19] 1915).

In both acute and chronic inanition, in adult rats, the testes lose at about the same relative rate as the body as a whole, the loss being slightly more marked in chronic inanition (Jackson,[18] 1915).

From the foregoing it appears that during inanition the testes have their strongest growth tendency just after birth, and that this tendency rapidly decreases with the age of the rat. The weaker growth tendency before birth is evidenced by the weight of the testes during prenatal inanition, which is only 16 per cent above that of the prenatal controls of the same body-weight.

Stewart (1919) gives the weight of the epididymides as 0.0016 gm. in the newborn rat, body-weight 5.08 gm. Hatai (1918) finds that the weight of the epididymides is 0.0025 gm. in the newborn, body-weight of 4.4. gm.; in my normal newborns the weight of the epididymides was 0.0012 gm., body-weight 4.92 gm. This weight is slightly below that given by Stewart and is less than half the value given by Hatai. This difference is probably due to a variation in technic used in cleaning the organ.

There were no male prenatal controls in Group 1 (Table 5).

In the other groups the absolute weight of the epididymides in the test rats is considerably above that of the prenatal controls, with the exception of Group 3, where it is 12 per cent below. The epididymides, however, average 17 per cent higher in the test rats of the various groups. This is about the same as the relation noted in the testes.

In postnatal inanition the epididymides, like the testes, show their strongest growth tendency shortly after birth (Stewart, 1918, 1919); this, however, disappears earlier in the epididymides than in the testes (Table 6).

Ovaries.—Jackson (1913) gives the weight of the ovaries in the newborn rat as 0.00078 gm., body-weight 5.0 gm. Stewart (1919) found their weight to be 0.00110 gm. in the newborn with a body-weight of 4.98 gm. In my normal newborns the weight of the ovaries was 0.00060 gm., body-weight 4.98 gm. This lower weight for the ovaries in my series is probably due to a variation in technic, since it is very difficult to free the ovary from its capsule and from the fallopian tube.

The data on the ovaries are somewhat irregular and conflicting (Table 5). In Groups 1 and 2 the absolute weight of the ovaries in the test rats exceeds that in the prenatal controls by 68 per cent and 6 per cent, respectively; in Group 3 it is 37 per cent below; in Group 4 it is 2.5 per cent above; in Group 5, 33 per cent below. The average weight is 1.3 per cent higher in the test rats. It is hazardous to draw any conclusions from such irregular data, but probably the ovary is very little affected by prenatal inanition.

It is interesting to note, however, that the ovaries in postnatal inanition, in general, show a tendency to increase in weight. This tendency is very slight shortly after birth, since in young rats kept at a constant birth-weight for sixteen days the ovaries showed a gain of but 5 per cent in absolute weight above the controls (Stewart, 1918*a*). In rats underfed from birth to three weeks the ovaries showed a gain of 83 per cent, and in rats starved from birth to ten weeks the gain is 54 per cent, (Stewart, 1918). In rats kept at a constant body-weight from three weeks to ten weeks of age the ovaries lose 27 per cent (Jackson,[19] 1915). In longer periods of inanition Stewart (1918) found a gain of 17 per cent in the weight of the ovaries, while Jackson[19] (1915) found a loss of 54 per cent. It should be remarked, however, that Jackson began the underfeeding at ten weeks instead of at three weeks, as in Stewart's series.

From these data it may be concluded that in prenatal life and up to a few days after birth, the growth tendency in the ovary during inanition is very slight; but that it soon reaches a maximum at a period between two weeks and three weeks of age, declining later.

Thyroid.—The Wistar norm (Donaldson, 1915) foı the weight of the thyroid gland is 0.00145 gm., or 0.027 per cent of the body-weight, 5.1 gm. Jackson (1913) gives the weight of the thyroid as 0.0012 gm, body-weight 5.1 gm. In my normal newborn series the thyroid weighed 0.0011 gm, or 0.022 per cent of the body-weight, 4.92 gm.

In my prenatal controls the weight of the thyroid forms 0.040 per cent, 0.030 per cent, 0.032 per cent 0.029 per cent, and 0.029 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus in the prenatal controls the thyroid forms a relatively higher percentage of the body-weight than in the normal newborn. Since the relative weight of the thyroid decreases as the birth-weight is approached, it is evident that the body as a whole is growing faster than the thyroid.

In my test rats the thyroid forms 0.024 per cent, 0.020 per cent 0.023 per cent, 0.021 per cent and 0.016 per cent of the body-weight in Groups 1 to 5, respectively (computed from Table 5). Thus in the test rats the thyroid has about the same relative weight as in the normal newborn rat and a lower relative weight than in the prenatal controls.

That the thyroid has been inhibited in its growth in the test rats is evident from a comparison of the absolute weights (Table 5). The absolute weight of the thyroid in the test rats is 33 per cent, 28 per cent, 11 per cent, 29 per cent and 45 per cent less than that in the prenatal controls in Groups 1 to 5, respectively. Thus, the absolute weight of the thyroid is lower in all the groups, the average being 29 per cent.

In postnatal inanition the thyroid exhibits a tendency to gain slightly in weight in rats held at maintenance from birth to sixteen days, or starved from birth to three weeks, or from birth to ten weeks (Stewart, 1918, 1919). In longer periods of starvation the thyroid loses quite markedly (Jackson,[19] 1915; Stewart, 1918).

In adult rats, during acute inanition, the thyroid suffers very little or no loss in weight, while during chronic inanition it loses relatively less than the body as a whole (Jackson,[18] 1915).

DISCUSSION

A comparison of the similarities and differences in the growth of the various organs and systems in both prenatal and postnatal inanition is so well shown in Table 6 that a detailed discussion is deemed unnecessary. However, special attention will be called to certain points.

In the systems (Table 6) the "remainder" is constantly above normal in weight in prenatal inanition, while in postnatal inanition it shows a definite loss at various periods throughout the life of the rat.

The visceral group as a whole is subnormal in weight during prenatal inanition. In postnatal inanition, however, it shows a marked tendency to gain in weight in the younger rats (underfed from birth to an average of sixteen days, and from birth to ten weeks, Stewart, 1918, 1919). When the underfeeding is begun at three weeks of age, the visceral group shows a slight gain or just maintains a growth equal to that of the controls. In cases of prolonged underfeeding in the young rats, under one year of age, and in adult life, the visceral group shows a decided loss. It should be noted, as before mentioned, that the gain or loss in the visceral group during inanition is dominated by a loss or gain in weight of certain large organs, such as the liver, lungs, gastro-intestinal tract, and brain. In postnatal inanition the gain in the visceral group compensates for the loss in the "remainder," while in prenatal inanition the converse is true. Thus it is evident that the strongest growth tendency manifested by the visceral group during inanition is at a period just after birth and that it becomes progressively weaker thereafter.

The musculature has a subnormal weight in prenatal inanition and shows but a slight gain (musculature and skeleton combined) in rats underfed from birth to an average of sixteen days of age (Stewart, 1919). It is in rats underfed from birth to three weeks of age that the musculature manifests its greatest gain. This tendency to gain is present, but weaker, in rats underfed for longer periods (Jackson,[19] 1915; Stewart, 1918). In both acute and chronic inanition in adult rats the musculature loses in about the same proportion as the body as a whole (Jackson,[18] 1915). It is evident, therefore, that the growth tendency in the musculature during inanition in the rat is weakest before birth, slightly stronger just after birth, and strongest at a period between birth and three weeks of age, declining thereafter.

The skeleton has a subnormal weight during prenatal inanition and shows a very slight gain in rats starved from birth to an average of sixteen days. In young rats underfed for longer periods, up to adult life, the skeleton shows a marked tendency to gain. During inanition in adult rats the skeleton shows very little change in weight. Thus the growth tendency manifested by the skeleton during inanition is weakest before birth and slightly stronger from birth to sixteen days of age. At three weeks of age, however, it is quite strong, increasing slightly toward adult life. It thus appears that the growth tendency manifested during inanition develops at a relatively later period in the skeleton than in the musculature, but persists longer in the former.

The integument manifests a moderately strong growth tendency during prenatal inanition and just after birth in rats underfed to an average of sixteen days of age. In rats underfed from birth to three weeks of age the integument shows no gain, and in rats starved for longer periods it shows a constant loss in weight.

In postnatal inanition the organs as a general rule manifest their strongest growth tendency in the youngest rats (underfed from birth to an average of sixteen days; Stewart, 1919). The liver, suprarenals and ovaries are exceptions to this rule. The liver loses markedly at this period as compared with a gain at later periods. The suprarenals and ovaries show a very slight gain as compared with marked gain in later periods.

With but few exceptions, those organs which show the most marked gain in the newborn rats (underfed from birth to sixteen days) during postnatal inanition are also above normal in prenatal inanition. The spinal cord is the only exception. Also, all the organs which show a loss or only a slight gain in the newborn rats during postnatal inanition (excepting the indefinite "remainder") are subnormal in weight in prenatal inanition.

It should be noted that the organs and systems that are above the normal weight in prenatal inanition have apparently a lower growth capacity than that shown in postnatal inanition just after birth (Table 6), while those organs and systems which are below normal weight in prenatal inanition (with the exception of the thymus) suffer a greater loss than in postnatal inanition. From the foregoing it is evident in general that the organs and systems of the rat have a weaker growth tendency during prenatal than during postnatal inanition.

The present investigations, therefore, emphasize the fact that in different periods in the life of the rat certain organs and parts react differently, as manifested by their growth during inanition. This is probably due mainly to the varying intensity of the normal growth tendency in the organs and parts at different periods.

Jackson and Stewart (1918) have called attention to the fact that during inanition in the rat the varying intensity of the growth tendency in the different organs and systems depends on four factors: (1) the duration of the period of inanition, (2) the age at which it occurs, (3) its severity, and (4) the character of the inanition.

In prenatal inanition the duration is known (period of starvation of mother). The age is known (length of gestation). The severity is apparently that sufficient to retard the growth of the entire body, an average of 40 per cent as compared with normal newborn controls. Attention may be called to the fact that some of the apparent differences in the growth tendencies of the organs and parts during prenatal and postnatal inanition may be due to the difference in the relative retardation of the body-growth. That is, while the body-growth (average) was retarded 40 per cent in prenatal inanition, it was retarded 66 per cent in Stewart's (1918*a*) series in starvation just after birth. The real nature of the inanition, that is, the amount of reduction in the various nutritive substances reaching the fetus during starvation of the mother, is unknown. The exact character of the inanition to which the fetus is subjected is, therefore, uncertain. However, from the nature of the changes in the relative weight of the organs and parts, it may be stated that the maternal organism during starvation in pregnancy makes extraordinary efforts, as is well known, to keep up the necessary supplies of nutritive substances to the growing fetus and thus protect it from the effects of inanition.

SUMMARY

1. Starvation instituted shortly after copulation in the female albino rat apparently results in an inhibition of pregnancy in the majority of cases. Whether this is due to an inhibition of the implanation, or to death of the ovum, has not been proved.

2. Of fifty-nine female albino rats starved from the eleventh day after copulation, early death of the fetus *in utero* occurred in three cases. Microscopic examination of the swellings in the uterine horns revealed a mass of degenerating tissue, with no evidence of any fetal structures.

3. The length of gestation in the mothers starved during the last half of pregnancy varied from twenty-one days to twenty-six days. Eight of the twenty-two total were above the twenty-three day normal limit, six with a gestation period of twenty-four days, one of twenty-five, and one of twenty six. The average period of gestation was twenty-three days, or one day above the normal average.

4. No abortions or premature deliveries were observed in any of the underfed rats.

5. Of a total of 120 newborn from mothers starved during the last half of pregnancy, forty-one were found dead after delivery. Whether these were dead *in utero*, or died during delivery or afterwards, is uncertain, since at birth they dropped through the wire bottom of the cage. Those living-born that were inclosed within the amniotic sac died of suffocation. Those found living seemed quite vigorous.

6. The average number of observed young per litter, from mothers starved during the last half of pregnancy, was 5.9. The normal average number of young per litter was 7.0 in 1,089 litters (King and Stotsenburg, 1915).

7. A condition of relative sterility apparently results in females starved during the last half of pregnancy. Of the total number starved but four became pregnant a second time.

8. The average weight of the newborn from mothers starved severely during the last half of pregnancy was approximately 3 gm., or 40 per cent below the normal birth-weight of 5 gm.

9. There was no constant relation between the percentage loss in weight of the mother and the weight of the newborn. In general, however, the largest females showed the largest relative loss in weight

and bore the largest young; and the weight of the newborn tends to be inversely proportioned to the severity of the starvation.

10. A prenatal norm for the various systems and organs was established by comparing the relative weights, at the various fetal stages, with those of the normal newborn.

11. During prenatal inanition the tail grows in length faster than the remainder of the body, thus giving rise to relatively long-tailed individuals.

12. Concerning the changes in the general body proportions during prenatal inanition, the head and limbs are slightly above normal weight, counterbalanced by a lower weight in the trunk.

13. The observations on the various systems are summarized as follows: The "remainder" has a weight 25 per cent higher in the test rats than in the prenatal controls. The integument shows a weight averaging 10 per cent above normal in the test rats. The musculature and moist skeleton are slightly subnormal in weight in the test rats, being 5 per cent and 7 per cent, respectively below the prenatal norm. However, the dried skeleton in the test rats has a weight 12 per cent above the prenatal norm. The visceral group, as a whole, has a markedly subnormal weight in the test rats, being 18 per cent below the prenatal norm. This is due chiefly to the subnormal weight of the liver and lungs. The low weight in the visceral group evidently compensates for the high weight of the "remainder."

14. The weight changes observed in the individual organs in the test rates during prenatal inanition, as compared with normal fetuses of the same body-weight, show the following average percentage differences in weight:

	Per cent		Per cent
Brain	+12	Intestines with contents	+15
Spinal cord	− 0.26	Intestines empty	− 2
Eyeballs	+31	Pancreas	− 0.26
Thymus	−21	Suprarenals	−52
Heart	+ 8	Kidneys	+ 6
Lungs	−39	Testes	+16
Liver	−45	Epididymides	+17
Spleen	+34	Ovaries	+ 1.3
Stomach with contents	− 4	Thyroid	−29
Stomach empty	+ 6		

15. In general, therefore, it may be stated that the spleen, eyeballs, epididymides, testes, and brain manifest a fairly strong growth

tendency during prenatal inanition, the tendency decreasing in the order named. A slight growth tendency is manifested by the heart, kidneys, stomach, and ovaries, decreasing in the order named. A retardation in growth during prenatal inanition increasing in the order named is shown by the pancreas, spinal cord, intestines, thymus, thyroid, lungs, liver, and suprarenals.

16. In general, the organs and systems that have been found to gain greatly during postnatal inanition (in the newborn rats) are, during prenatal inanition, also above normal weight, but to a much less degree; while those below or but slightly above normal weight during postnatal inanition show a still greater loss in prenatal inanition. Thus, during inanition, the growth impulse of the organs appears as a rule weaker in the prenatal than in the postnatal period. It should be noted, however, that the exact nature of the prenatal inanition is somewhat uncertain.

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